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ORIGINAL ARTICLES

CLINICAL FEATURES OF PATENT DUCTUS ARTERIOSUS WITH SPECIAL REFERENCE TO CARDIAC MURMURS

By Samuel A. Levine, M.D.
and
Albert E. Geremia, M.D.
Boston, Massachusetts

(From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School)

Now that certain types of congenital heart disease may be treated successfully by surgery, accurate diagnosis is no longer a purely academic or intellectual endeavor. Until a few years ago many physicians were satisfied if they could establish the fact that a given heart was diseased or abnormal. A smaller number would succeed in deciding that a cardiac abnormality, when present, was congenital, but only a few felt competent to make an accurate anatomic diagnosis of the abnormality. To be sure, with increasing interest and largely through the stimulus of painstaking work of the late Maude Abbott, knowledge concerning congenital heart disease was becoming more general and more definitive during the past 2 decades. Until the splendid report of Gross and Hubbard,[7] of the surgical treatment of patent ductus arteriosus, it remained a matter of no great consequence whether the exact anatomic lesion could be recognized, when congenital heart disease was present. Therapy was very limited, consisting mainly of hygienic and of symptomatic procedures, the occasional use of phlebotomy and oxygen, and combating or preventing infections. With the introduction of surgical treatment, the situation has entirely changed. Already many cases of patent ductus arteriosus have been cured,[7,8] patients with tetralogy of Fallot have been helped,[1,2] coarctation of the aorta has been relieved by operative methods,[5] and finally constriction of the trachea from congenital vascular ring or right aortic arch has been treated successfully.[6] It is therefore necessary for physicians to become more familiar with the means of accurate diagnosis of congenital heart disease.

Inasmuch as simple bedside findings will always remain the bulwark of clinical diagnosis, it seemed appropriate to review a group of well-authenticated cases of patent ductus arteriosus and analyze some of the features they presented, particularly those obtained by auscultation. It is clear, that in the great majority of instances, the finding that initiates any consideration on the part of the physician of the possibility of patent ductus arteriosus will be the detection of a cardiac murmur. It is well known that the classical "machinery murmur" in the pulmonary area is fairly characteristic of patent ductus arteriosus. It has become quite evident, however, that with increasing experience the murmur is by no means

always characteristic and often has no machinery quality. It is now necessary to recognize cases that display atypical murmurs and to become familiar with the general range of the loudness and the peculiarity of the murmurs. One might ask whether patent ductus arteriosus may ever be present without any murmurs at all, or with only a systolic component.

that 11 were of Grade 3 intensity, and 1 was even called Grade 2−. This means that many cases showed what ordinarily is designated as a moderate systolic murmur and that rarely only a slight murmur was present. In 21 instances the intensity of the diastolic component was carefully noted preoperatively and the average intensity was found to be Grade 3.1. In

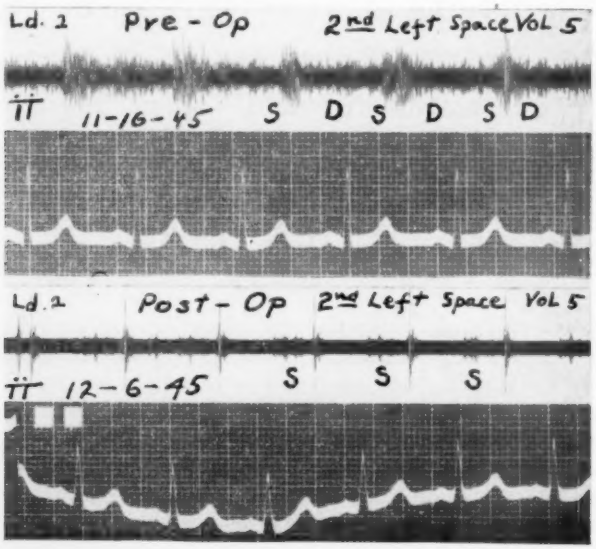

FIG. 1.—Phonocardiogram (pulmonary area) and electrocardiogram (Lead 2), before and after section of patent ductus. Note continuous murmur (above) with accentuation at end of systole (S) and beginning of diastole (D). Clinically it was of Grade 6 intensity. After operation only a faint systolic murmur (S) remains.

MURMURS. For this purpose 37 cases of patent ductus arteriosus, in which the diagnosis was confirmed at operation by Dr. R. E. Gross, were analyzed. All but 1 of these were over 12 years old, the age ranging from 7 to 47 years, the average being 24 years. Our first interest was the intensity of the murmur. The loudness was indicated by gradations 1 to 6, according to the suggestion reported in an earlier publication.[10] In 25 instances in which accurate estimation of the intensity of the murmur by a competent observer was made preoperatively, the average intensity of the systolic component was found to be 4. It is of considerable interest

no instance was the diastolic component louder than the systolic, occasionally it was of the same intensity but generally it was fainter by 1 or more gradations. A peculiarity commonly observed was that the murmur appeared to become louder during the latter part of systole, enveloping the second heart sound, and continuing with decreasing intensity during diastole* (Fig. 1). In 5 cases the diastolic murmur was faint enough to be called Grade 2, and in 1 instance it was only Grade 1 (Fig. 2). In fact, the diastolic murmur in this latter case was so faint that it could be detected only after prolonged and undisturbed auscultation.

* Dr. John P. Hubbard called our attention to this peculiarity several years ago.

Although there was no instance in this series in which no murmur at all could be heard, rare cases of this type have been reported[9] (Case 3). In another instance the murmur was found to disappear during the last month before death.[4]

The murmur was generally loudest in the so-called pulmonary area (second left interspace) but occasionally had its maximum intensity in the first or third left interspace. When it was very loud it was widely distributed, so that it could be

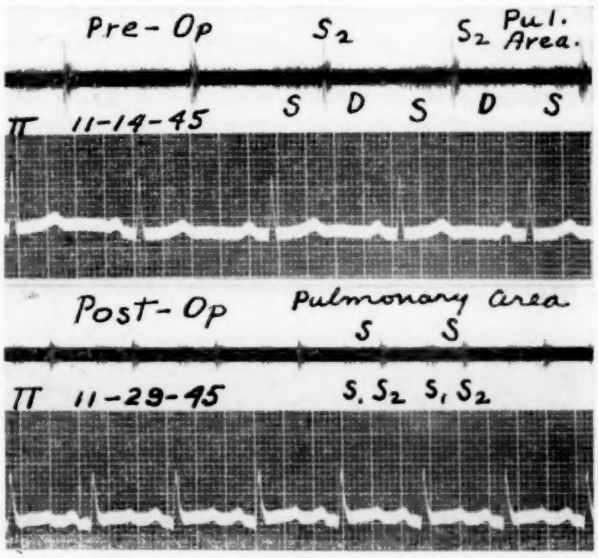

FIG. 2.—Clinically the systolic murmur was Grade 2 and the diastolic Grade 1 in intensity preoperatively and only Grade 1 systolic and no diastolic postoperatively. Note that the phonocardiograms show faint murmur. (S = systole, D = diastole, S_1 = first sound, S_2 = second sound.)

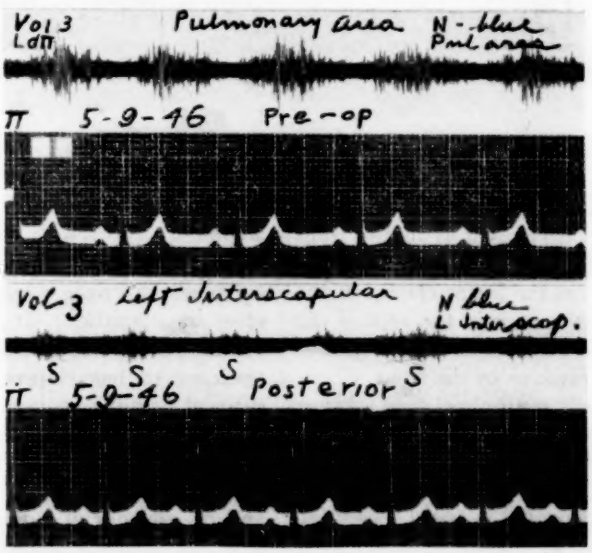

FIG. 3.—Note loud murmur in pulmonary area (Grade 5) is crescendo and diminuendo "around" the second heart sound. Murmur, though faint, can be well heard in the left interscapular region.

heard throughout the back of the chest and even at times down the arm, to the olecranon process of the elbow (Fig. 3). It is clear, therefore, that its detection in the back was merely a reflection of its intensity and did not indicate a concomitant coarctation of the aorta. Attention is called to this observation because the presence of a systolic murmur in the interscapular region has at times been regarded as evidence of coarctation of the aorta. In a rather extensive study of cardiac murmurs it has become apparent that any loud murmur (Grades 5 and 6) can be heard clearly in the back and that the characteristic of coarctation of the aorta is the fact that the murmur is almost as loud in the back as it is in the front of the chest (Fig. 4). The reason for this is obvious, for in the latter condition the origin of the murmur is in the arch of the aorta, which is deep in the chest, almost as near to the back as to the front.

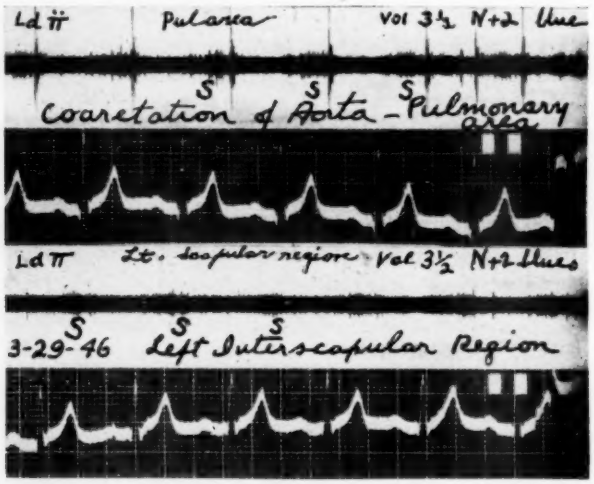

FIG. 4.—Note that in coarctation of the aorta the systolic murmur (S) is only a little louder in the front of the chest than in the back. Contrast this with Figure 3.

Apical systolic murmurs were always present in these cases. It is difficult to know whether these apical systolic murmurs had an origin other than the patent ductus arteriosus, for in most cases the basal murmurs were loud enough to be transmitted to the apex. In all, an apical systolic murmur was present which generally was of Grade 2 intensity, but occasionally fainter or louder (Grade 1 or Grade 3 to 4). It is of interest that in some patients the continuous systolic and diastolic murmur (though fainter) was also present at the apex, and in 4 cases a definite mid-diastolic murmur was audible, quite unlike the diastolic murmur heard in the pulmonic area and resembling a murmur of mitral stenosis. This murmur may very likely be due to the rapid inflow of blood from auricle to ventricle in early diastole.

After a successful operation one would expect the murmurs due to patent ductus arteriosus to disappear. Although this is commonly the result, it is by no means invariable. In the majority of instances no murmurs were present several days after the operation. It is not possible to examine many cases satisfactorily until a week or so has elapsed because of the surgical dressings covering the chest. In a few, postoperative pericarditis produced a to-and-fro pericardial friction rub which somewhat imitated the preoperative to-and-fro murmur of patent ductus arteriosus. In others a slight systolic murmur persisted in the pulmonary area for a few

days and then disappeared in about 2 weeks. During 1938 and 1939 when the duct was ligated rather than divided, there were isolated cases of recanalization with consequent reappearance of the continuous murmur. When this occurred, the murmur was less loud than the original one. There is also an instance in which a systolic and diastolic murmur persisted along the left upper sternal border. This occurred in a case of subacute bacterial endocarditis in which vegetations were found on the aortic valve

functional basal systolic murmurs. It is apparent that the persistence of a slight systolic murmur is not to be regarded as evidence of inefficacy of the operation. The persistence of a basal systolic and diastolic murmur may be interpreted in 1 of several ways: namely, recanalization of the duct, the presence of bacterial endocarditis of the aortic valve or an additional anatomic lesion such as coarctation of the aorta or some other congenital abnormality. It is of interest that a diastolic murmur did not persist in any case in this

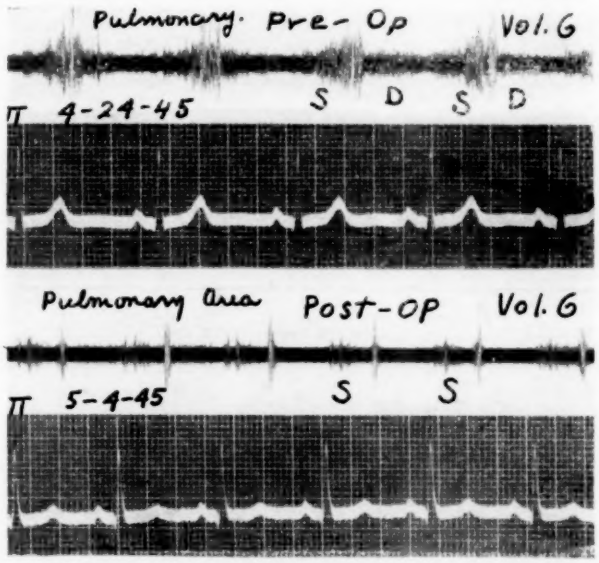

FIG. 5.—Typical case of patent ductus before and after successful operation, showing persistence of a Grade 2 pulmonary systolic murmur.

though the ductus had been ligated successfully. The most significant observation in the postoperative study was the fact that the slight pulmonic systolic murmur (Grades 1 and 2) may persist for a considerable time after successful division of the ductus (Fig. 5). Although such murmurs may disappear within a week or 2, they also may persist as long as 15 months. Such basal systolic murmurs may possibly be explained on the basis of continued dilatation of the pulmonary artery or may have the same debatable significance ascribed to other inconsequential or

series after successful division of the duct except for the occasional instance of bacterial endocarditis involving the aortic valve.

THRILLS. A definite palpable systolic thrill was present in 21 of the 37 cases. This was maximum in the second and occasionally in the first left interspace. It was always systolic in time but occasionally continued well into diastole. In a few instances, especially in thin-chested individuals, where the murmur was very loud, the thrill was palpable over most

of the precordium, and even extended above the clavicle.

Blood Pressure. A review of the blood pressure readings before and after operation confirmed what is quite well known, namely, the pulse pressure is increased in patent ductus arteriosus, and the levels return to normal after treatment. The average preoperative reading in this series was systolic pressure 122.5 mm. Hg and diastolic 57.3 mm. Hg and the corresponding postoperative readings were 124 mm. and 78.5 mm. The pulse pressure, therefore, decreased from an average of 65.2 mm. to 45.5 mm. Hg. The range of the preoperative systolic levels was from 90 mm. to 172 mm. and the diastolic from 0 to 82 mm. The corresponding postoperative range was from 100 mm. to 170 mm. systolic and 50 to 84 mm. diastolic. It is of interest that the average systolic pressure was not altered by the operation, but the diastolic rose 20 mm. Hg. Although low diastolic pressures are characteristic of this condition there were exceptional instances in which the diastolic pressure was as high as 75 mm. and even 82 mm., when the systolic level was not over 110 mm. Hg

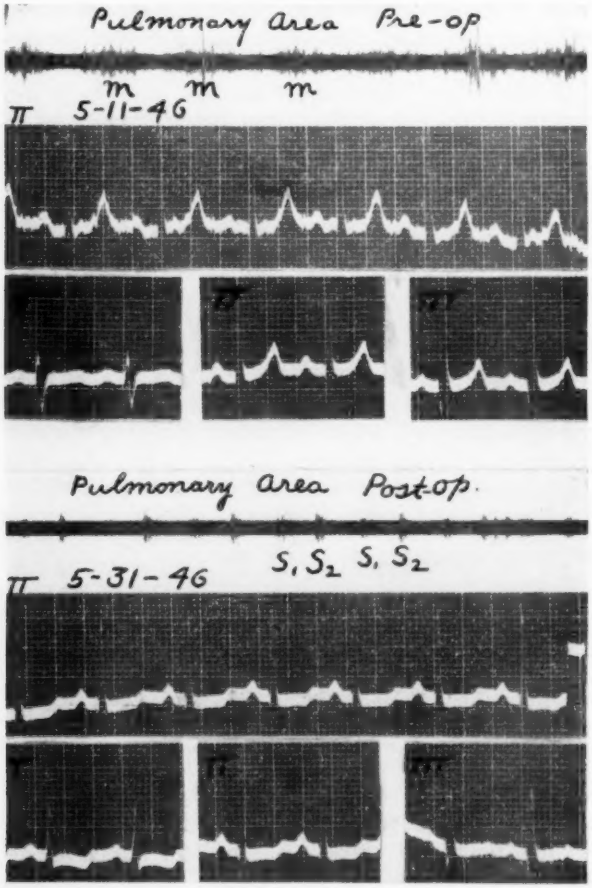

Fig. 6.—Exceptional case showing right axis deviation in the limb leads before operation and normal axis after operation. The continuous murmur disappeared.

ELECTROCARDIOGRAMS. There were 34 cases in which preoperative electrocardiograms were available for study. The most important observation was that right axis deviation was found in only 1 instance (Fig. 6). Four showed left axis deviation, the others had a normal electrical axis. Sinus arrhythmia was present in 9, premature ventricular beats in 3, premature auricular beats in 2, intraventricular block occurred in 2 and a short P–R interval measuring 0.12 second with a QRS of 0.08 second in 1 case. There were 2 in which the ventricular complexes were decidedly abnormal, with inversion of the T waves in Lead 1 and Lead 2 not due to digitalis. The only electrocardiogram changes that took place postoperatively were those that could be ascribed to an associated pericarditis and accumulation of pericardial fluid that may follow the operation. Some developed a lowering or flattening of the T waves in Lead 1 and Lead 2 and in a few instances the T waves became slightly inverted. In several cases tracings taken some months later showed complexes tending to return to a preoperative configuration.

SYMPTOMS. The presence or absence of symptoms and the type of complaints among these cases were studied. Despite the fact that there was no evidence of right to left shunt or any other congenital abnormality apart from patent ductus arteriosus in any of these cases, 3 were said to have been a "blue baby" at birth. No significant limitation of physical activity was present in 31 of the 36 cases. The other 5 had slight to moderate restriction in activity because of varying symptoms such as breathlessness, fatigability and palpitation. Breathlessness on effort of a slight to a moderate degree occurred in 14 cases, 2 of which also complained of orthopnea and an additional one had paroxysmal nocturnal dyspnea. For the most part, when shortness of breath was a complaint it consisted of a feeling of breathlessness on running, playing or climbing stairs. In some cases these symptoms developed only in the last months or year before operation. Pain in the precordium was quite common, occurring in 12 patients. This did not have the character of anginal pain, generally was localized in the left breast or apical region and was either of a stabbing momentary nature or consisted of a mild steady ache. It was not constricting or sternal in type. Palpitation was common in these patients, occurring in 16 instances. Fainting spells were noted in 2 and faint cyanosis in 3 of this series. A past history of rheumatic fever was striking by its absence in this group, though 3 had a past history of nosebleeds and 1 of growing pains.

An attempt was made to correlate the diameter of the duct as estimated by the surgeon with the loudness of the systolic component of the murmur.[1] The cases were divided into 2 groups, those in which the systolic murmur was of Grade 4, 5 and 6 intensity and the remainder of Grade 2 or 3 intensity. The average diameter of the former was 11.6 mm. and of the latter 9 mm. There was enough overlapping of the 2 groups, however, to make it impossible to predict the size of the patency by the intensity of the murmur. As an illustration of this difficulty it was found that in 1 case, with a Grade 5 systolic murmur, the diameter of the duct was 6.5 mm., while in 2 other instances with Grade 3 murmurs the diameter was 15 mm. It is obvious that many factors come into play such as thickness of the chest wall, hyperactivity of the heart beat and differences in pressure in the aorta and pulmonary artery. Possibly the length of the duct apart from its width may affect the loudness of the murmur.

Comment. The development of surgical methods of treatment for various types of congenital heart disease necessitates accurate anatomic diagnosis. The general physician, who will ordinarily be the starting point in any diagnostic investigation, will have to become more alive to the importance of hitherto immaterial abnormal findings. The detection of cyanosis and clubbing of the fingers is generally easy and obvious. The finding

of cardiac enlargement is often difficult and only to be established accurately by Roentgen ray examination. For that reason it will be overlooked frequently. The presence of cardiac murmurs, however, can be determined quickly by any practitioner, even if the interpretation may be difficult. For this reason, an analysis of 37 authenticated cases of patent ductus arteriosus was made to determine some of the characteristics of the murmurs present.

It can be said that all cases had murmurs, best heard in the pulmonary areas. Generally the systolic components were moderately loud or quite loud (Grades 3 to 6). The diastolic element was about

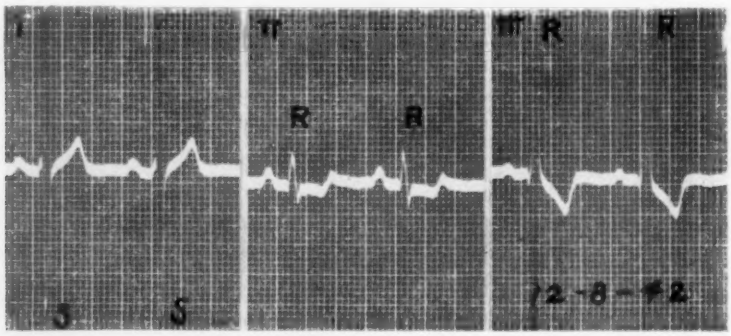

FIG. 7.—Rare case of patent ductus with marked right axis deviation. S and R indicate depth and height of the respective waves. Autopsy showed marked pulmonary arterial disease in addition to patent ductus. Patient was 37 years old.

1 gradation fainter, though in this series every one had some diastolic element. There is reason to believe that rare cases of patent ductus exist in which no murmurs or at least no diastolic murmurs may be audible. One case, not included in this series, has been studied having only a systolic murmur in which, though a significant patent ductus was present, the pulmonary arteries were so diffusely involved and the pulmonary arterial pressure so elevated that there was every reason to believe little, if any, flow was taking place through the patent ductus. Moderate cyanosis was present in this case and arterial oxygen saturation which was decreased to 82% rose to 100% after inhalation of 100% oxygen. This latter test proved that the decreased arterial saturation was not due to a right to left shunt of venous blood into the arterial system, as that would not have been influenced by inhalation of 100% oxygen. It must have been due to changes in the diffusion of oxygen in the lungs, similar to that observed in emphysema. This case showed marked right axis deviation in the electrocardiograms (Fig. 7). It should be emphasized that occasionally the diastolic component of the murmur in the pulmonary area is so faint that it can easily be overlooked (Fig. 2).

Isolated cases of authenticated patent ductus have been reported in which no murmurs whatever were present. Case 3 of the series reported by Keys and Shapiro[9] was of this type. This 46 year old woman died of congestive heart failure. The blood pressure had been 142/40. The heart weighed 700 gm., and showed marked right ventricular and some left ventricular hypertrophy. A patent ductus 2 cm. long and 1.5 cm. wide was present without other congenital abnormalities. There was marked sclerosis of the ductus and pulmonary artery. The latter and its branches were also considerably enlarged. A plausible explanation of the absence of murmurs was that the pressure in the pulmonary artery was as great as in the aorta and therefore there was no flow

through the duct. There are also rare instances in which the characteristic murmur was noted to disappear in the last weeks of life.[4] Here also a change in the dynamics of the circulation with severe heart failure may possibly account for the lack of flow through the duct.

Apical systolic murmurs were also invariably present in these cases of patent ductus arteriosus. Occasionally a short faint mid-diastolic murmur was present at the apex suggestive of mitral stenosis. These murmurs either disappeared entirely after successful operation on the ductus or there remained a slight pulmonary systolic murmur. The latter might persist for days or weeks and probably is due to the continued dilatation of the pulmonary artery or to the same indefinite mechanism involved in many inconsequential pulmonary systolic murmurs heard in healthy young individuals. When a basal diastolic murmur persisted after operation it was found to be due to recanalization of the ductus (in a few of the early cases in which the duct was ligated and not divided) or to bacterial endocarditis which had also involved the aortic valve.

Electrocardiograms proved very helpful in diagnosis. Despite the fact that right axis deviation is very common in various forms of congenital heart disease, there was only 1 instance in which definite right axis deviation was present (Fig. 6). In this case it was thought at first that another congenital abnormality was present in addition to the patent ductus. The fact that all murmurs disappeared after operation and no other evidence was elicited of further cardiac disease, the right axis deviation was thought to be due to concomitant pulmonary arterial disease and pulmonary hypertension. It is apparent, however, that the finding of right axis deviation should make one strongly suspect that the diagnosis of patent ductus is incorrect or that the patient has an additional lesion, such as pulmonary stenosis.

The diagnostic problem in exceptional cases may be very difficult. One instance, not included in this study, illustrates some points of interest. This young boy of 11 years had the classical machinery murmur at the base of the heart. The unusual feature was that it was much louder at the aortic than the pulmonary area. It was quickly surmised that he might have a persistent right aortic arch. The electrocardiogram, however, showed well-marked right axis deviation. At this point the diagnostic problem became too involved and it seemed advisable to study the problem by catheterizing the heart. This was done by Dr. Lewis Dexter[3] and he was able to make a definite diagnosis of pulmonary stenosis, patent ductus arteriosus and right aortic arch. This was a very vital examination as it indicated not only that the ductus should not be sectioned, but that the congenital abnormality required that short circuit. The new operation devised by Blalock and Taussig had already been functioning in this case. If the ductus had been sectioned the boy could not have lived or at least the condition would have been made much worse.

Conclusion. A study was made of 37 verified cases of patent ductus arteriosus with special emphasis on the auscultatory findings before and after operation. The detection and proper interpretation of the murmurs are most important in diagnosis. Great variation in the intensity of the murmur was found and many failed to show the classical machinery character. In some the auscultatory findings were very inconspicuous.

Electrocardiography is indirectly helpful in diagnosis as only 1 case showed right axis deviation.

In doubtful or puzzling cases catheterization of the heart will be necessary to establish an accurate and definitive preoperative diagnosis. Only in this way will some cases avoid harmful surgery.

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INFECTIOUS HEPATITIS: CLINICAL AND LABORATORY FEATURES OF 295 CASES

By Hyman J. Zimmerman, Capt., M.C.*
Charles F. Lowry, Lt. Col., M.C.
Kahn Uyeyama, Major, M.C.
and
Raymond Reiser, 1st Lt., San. C., A.U.A.

There have been excellent reviews of infectious hepatitis written by many prominent authorities. Although epidemics of the disease have been described for over a century, during the present war it has come into special prominence because of the high incidence among both civilian and military populations in all parts of the world. Infectious hepatitis is now thought to be caused by a virus. Present evidence suggests that transmission of the disease in epidemics may be by way of the gastrointestinal tract, although the respiratory tract as the important portal of invasion has been suggested. It is considered a systemic infection with the most prominent symptoms referable to the liver. While benign and rarely the cause of death, the disease can produce disablement for extended periods. This study is presented to illustrate the clinical features, laboratory data, treatment, and criteria for disposition of a group of cases of infectious hepatitis.

Procedure. This report is based on a study of 295 cases admitted to a general hospital in eastern France between February 15 and June 14, 1945. All patients were isolated. On the day after entry, the blood count, icterus index and urine examinations were performed. Blood icterus determinations and pigment studies of the urine were repeated at 3-day intervals throughout the hospital stay.

Other laboratory studies were performed as indicated. Patients were seen by the medical officer daily, and change in physical status and symptomatology noted at frequent intervals. Length of hospitalization was determined by the clinical and laboratory features as well as by exercise tolerance as determined by a standardized reconditioning program. All patients were given a diet high in protein (2 grams per kilogram of body weight daily) and low in fat (less than 35 grams daily), the total caloric value being 2500 daily. The protein intake was supplemented by feedings between meals of skimmed milk enriched with egg albumin. Cooperation of the patients in partaking of this diet was excellent. Plasma was given liberally to patients who appeared severely ill or who were unable to eat. Patients were followed until discharge to duty. If after 60 days of hospitalization, recovery was incomplete, it became necessary to evacuate them from the theatre of operations.

Clinical Features. A number of different disease patterns were noted. The types and distribution are shown in Table 1.

Although the dominant form recognized was acute hepatitis with jaundice, which included all cases with icterus index above 12, a number of cases without jaundice were seen. Save for the milder course and the absence of jaundice in the latter, the two groups were identical. In patients with jaundice, the severity and duration of the illness was roughly proportional to the intensity of the icterus. A classification based on the intensity of jaundice is presented (Table 2).

Persistence of activity of the disease beyond 60 days was arbitrarily called subacute hepatitis, as this period was the

* Present address George Washington University Medical Division, Ballinger Municipal Hospital, Washington, D. C.

maximum allowed for retention of patients in the theatre of operations. Although the tendency for this to occur varied with the peak icterus, even in the presence of hepatitis without jaundice it occurred in one-third of the patients.

The incidence of icterus of various intensity is shown in Fig. 1. The greatest number of patients fall in the range 40 to 49, with decreasing incidence at higher and lower levels. From this frequency distribution curve we are led to believe that the apparent incidence of hepatitis without jaundice is fairly represented at being in the neighborhood of 10%.

cases. Several other patients gave a history of isolated cases in their organizations antedating the general dissemination of the disease throughout the unit by 4 to 6 weeks.

ONSET. Although prominent in the onset of the disease was the well-known tetrad of anorexia, lassitude, epigastric distress, and dark urine, it was noted that the types of onset could be sharply categorized. While in two-thirds of the group the disease was ushered in with an array of symptoms suggesting influenza, in half of these patients the true diagnosis was suggested by the accompanying abdominal

TABLE 1.—CLASSIFICATION OF DISEASE PATTERNS

Disease Pattern Seen	Number of Cases
1. Hepatitis, acute infectious, with jaundice	260
A. With recovery within 60 days	142
B. With residual subacute hepatitis after 60 days	83
C. With relapse	35
1. With jaundice	14
2. Without jaundice	21
2. Hepatitis, acute, infectious, without jaundice	35
A. With recovery within 60 days	24
B. With residual subacute hepatitis after 60 days	4
C. With relapse	7
1. With jaundice	3
2. Without jaundice	4

TABLE 2.—CLASSIFICATION OF DEGREE OF SEVERITY BASED ON INTENSITY OF ICTERUS

Categories	Range of Icterus Index	Total Number of Cases	Number Requiring Over 60 Days	
			Number	Per Cent
Very severe	Over 100	9	9	100
Severe	70–100	26	23	80.7
Moderate	40–70	111	50	45.0
Mild	10–40	114	36	31.6
Non-icteric	Below 10	35	11	31.3

INCUBATION PERIOD. Incubation period as estimated from this series falls into the accepted 3- to 6-week range Two of the patients had been in this theatre of operations for only 5 weeks and with a unit in which an outbreak of hepatitis occurred, for only 25 days. Another group of patients were members of the organization which began drinking unchlorinated water directly after arrival at a new area; during the following few days many cases of diarrhea appeared, and 3 weeks later the first case of jaundice was noted, following shortly thereafter by a number of other

symptoms and dark urine. In the remainder of this group a few days elapsed before evidence of hepatic involvement was noted. In the patients showing an insidious onset, it was not uncommon for the first complaint to be dark urine, although the debilitating malaise and severe anorexia were usually more prominent. The small group complaining mainly of abdominal pain and anorexia were occasionally diagnostically troubling and at times simulated appendicitis or even renal colic.

SYMPTOMS. The frequency of various symptoms on entry are shown in Table 4.

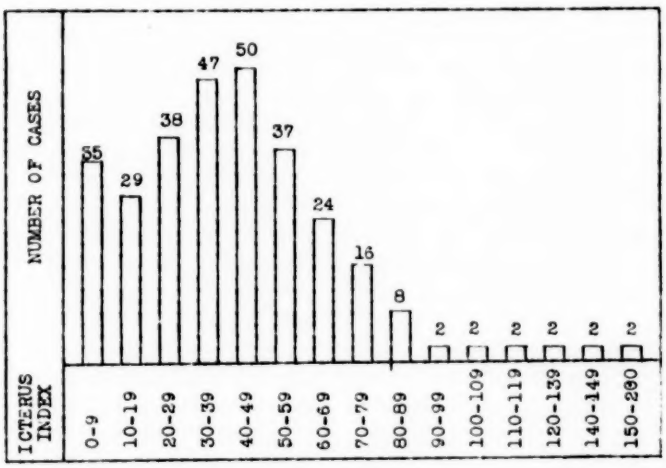

FIG. 1.—Distribution of peak icterus.

TABLE 3.—TYPES OF ONSET OF HEPATITIS IN 295 CASES

Types of Onset	Number of Cases	Per Cent
Influenzal (sudden onset, chills or chilly sensations, generalized aching, fever, headache, with or without respiratory symptoms)	95	32.2
Influenzal systemic symptoms with simultaneous signs and symptoms referable to the liver (fever, generalized aching, headache, anorexia, nausea, abdominal pain, dark urine)	99	33.6
Insidious (malaise, lassitude, anorexia, nausea, abdominal pain, dark urine)	86	29.2
Abdominal pain simulating the surgical abdomen	15	5.1

TABLE 4.—SYMPTOMS AND SIGNS ON ENTRY IN 260 CASES OF HEPATITIS WITH JAUNDICE

Symptoms	Number of Cases	Per Cent
Anorexia	250	96.2
Dark urine	245	94.1
Malaise	242	93.7
Nausea	211	80.8
Pain	178	68.4
Chilly sensations	159	60.9
Headache	148	56.8
Fever	138	52.2
Epigastric "lump"	125	48.0
Vomiting	97	37.4
Heartburn	71	27.4
Constipation	66	25.5
Itching	60	23.0
Alternating constipation and diarrhea	53	20.1
Respiratory symptoms	53	20.1
Chills	42	14.2
Diarrhea	37	12.5
Light stools	32	12.1
Dysuria	30	11.9

Signs	Number of Cases	Per Cent
Clinical jaundice	236	90.2
Skin and sclerae	210	80.0
Sclerae only	26	10.2
Tenderness in RUQ or epigastrium	223	85.7
Enlarged liver	180	69.1
Adenopathy	199	76.5
Generalized	101	38.9
Cervical only	98	37.6
Enlarged spleen	51	21.2
Bradycardia	105	40.2
Fever	188	72.0
Rash	3	1.1
Herpes labialis	6	2.2

The same relative frequency was noted in patients without jaundice, save that in the latter dark urine was rarely described. In all, anorexia was almost invariable and usually severe. Abdominal pain was described by most patients as dull and leaden, by a few as sharp and colicky. Although usually noted as epigastric or right upper quadrant pain, it was frequently generalized. Many patients felt as though they had a "lump" in the epigastrium. A number complained of pain or a "tired" feeling in the back.

Dark urine was frequent, but only 1 patient in 8 reported light stools. Transient burning dysuria was occasionally noted. Six patients in 10 complained of disturbed bowel function, either diarrhea, constipation, or both. Headache, complained of on entry by 70% of the group was described by most as orbital or frontal; frequently the orbital pain was "burning", and patients noted aggravation of the pain on eye movement.

About half of the patients with an influenzal type of onset had rhinorrhea, a few sore throat, and an occasional one complained of a cough. Most patients, however, suspected of having respiratory disease were under suspicion because of an undiagnosed febrile syndrome, rather than because of significant respiratory involvement. Five per cent of the group were admitted with a Roentgen-ray-verified diagnosis of primary atypical pneumonia.

Itching was noted on entry in 20% of the group. Transient urticaria was reported by 3 patients, labial herpes by 6 others.

Signs. The liver was palpably enlarged on entry in two-thirds of the group, averaging 2 cm. below the right costal margin; occasionally in extremely jaundiced patients it was at the level of the umbilicus. It was noted that often when the liver edge could not be felt in the right upper quadrant, careful palpation in the epigastrium demonstrated its enlargement.

Adenopathy, either generalized or cervical only was common. Barker[1] has placed some emphasis on the diagnostic helpfulness of a single enlarged node behind the right or left sternocleidomastoid muscle, but such limited adenopathy was found in only one patient. The nodes were usually small, averaging 1 cm., rarely twice this size, always soft and only slightly tender. The spleen, moderately enlarged in one-fourth of the group, was firm and nontender.

Moderate bradycardia was noted in 40% of the group on entry, while fever, ranging from 99° F. to 101° F., was present in 70% of the patients. Occasionally it was higher, especially in the pre-icteric patient, rarely reaching 105° F. Clinical jaundice was noted on entry in 90% of the patients showing an elevated icterus index; of these one-ninth had scleral icterus only. Of the group not jaundiced on entry, a few had icterus indices between 10 and 13 at the peak; the remainder were pre-icteric on entry, developing their jaundice while in the hospital. These patients on entry were indistinguishable from the group classified as hepatitis without jaundice.

Skin lesions on admission were rare. Two patients showed a faint macular erythema of the face and chest and in 1 patient a papular eruption of the arms and trunk was noted.

Course and Duration. Symptoms observed during the hospital stay were essentially the same as those reported on entry. In general the abdominal pain, anorexia and headache complained of during the pre-icteric period decreased in intensity with the development of jaundice, but pain in the epigastrium, right upper quadrant, or small of the back persisted for 4 or 5 weeks in most patients. Pain and tenderness in one or both lower quadrants was noted in 10% of the group at some time during the hospital stay. Malaise and anorexia subsided gradually, the malaise often being the last symptoms to leave. Bloating was described by almost all patients during the 3rd, 4th and 5th weeks of hospitalization.

Itching, noted in only 20% of the group on entry; was complained of at some time during the course by 70% of the patients. Although mild and transient in most cases,

in a few patients it was severe and intractable for 3 or 4 days.

The liver usually remained palpable and tender as long as pain persisted. Jaundice receded at a rate paralleling the blood icterus decrease.

Duration of signs and symptoms, although roughly proportionate to the intensity of the peak icterus, showed a certain constancy. In 50% of the mild group there was disappearance of clinical and laboratory evidence of continued activity by the 5th week. Twenty per cent required 6 weeks for complete remission, while the remainder continued to present symptoms after 60 days of hospitalization. The shortest recovery period seen in patients with icterus in the higher brackets was 6 weeks. The proportion of patients in each group not recovering within 60 days has already been shown (Table 2). Patients showing hepatitis without jaundice required approximately the same length of time for recovery and showed the same tendency to pass into the subacute stage as the group classified as mild.

Criteria used to determine recovery were modeled on those set forth by Barker[1]. There included absence of pain or bloating, return of a feeling of well-being, absence of epigastric or right upper quadrant tenderness, subsidence of hepatomegaly (or if the liver remained enlarged, absence of tenderness) and presence of normal appetite. Laboratory evidences were a normal sedimentation rate, normal icterus index for at least 2 weeks and urobilinogen in the first morning urine below the level of 2.0 mg. per 100 cc. With these criteria satisfied, the patients were subjected to an increasingly rigorous 10-day program of physical exercise. If all of the above features remained unchanged, the patient was ready for discharge to duty, without fear of relapse. Failure to adhere rigidly to all of these criteria early in the program necessitated re-admission of a number of patients who relapsed after being returned to duty. (See Case 123.)

Relapses. Most relapses were apparently due to excessive activity when the patient should have been at rest, too early reconditioning, or intercurrent infections. There were, however, several cases which relapsed in the absence of any of these factors. In this group of 295 patients, relapses occurred in 43 cases, that is, 1 in every 7. There was no apparent correlation between the intensity of the original attack and the incidence of relapse, nor between the presence of intensity of jaundice in the original attack and the presence or height of icterus in the relapse. One out of every 4 relapses was accompanied by jaundice. Three patients with typical bouts of acute hepatitis without jaundice, after 3 or 4 weeks of uneventful convalescence, relapsed and this time developed distinct icterus.

In most cases the relapse was shown by return, after a symptom-free interval of a week or more, of pain, malaise and anorexia, and was verified by return of or increase in adenopathy and in size and tenderness of the liver. Laboratory correlation was found in return of, or increase in, urobilinogenuria, increase in serum globulin, and elevated sedimentation rate. When jaundice developed during a relapse, return of icterus index to normal proceeded more slowly than in the initial attack.

Relapses were noted as early as 3 weeks and as late as 3 months after the initial attack. There were never more than 2 weeks of complete well-being between the end of the initial attack and the onset of the relapse.

Complications. No deaths were noted in this series. In 6 cases, however, the picture said [1.5] often to herald a fatal outcome was noted. This included sudden return of fever, extreme lethargy and drowsiness, severe nausea and vomiting. All 6 had been deeply icteric, but the time that this picture appeared varied from 1 to 4 weeks after the time of peak icterus. To all such patients plasma and, at times, intravenous glucose were given liberally until definite improvement occurred. In addition to the above group, 21 patients showed transient behavior changes characterized by irritability, querulousness, drowsiness, insomnia, and tremors. One patient developed an apparently typical

Guillian-Barre syndrome during the 4th week of the disease.[16]

It was noted that resistance to respiratory disease seemed slightly impaired in the patient convalescing from hepatitis. In 46 patients, about 15% of the group, mild episodes of nasopharyngitis developed. Three other cases developed follicular tonsillitis.

Gingivitis was noted in 13 cases. Skin petechiae were observed in only 2 patients. Melena was noted in 3 cases and epistaxis in 2. Thirty-three patients developed of symptoms. Rate of decrease of icterus was fairly constant and time required for return to normal is roughly dependent upon the peak achieved (Fig. 2). The longest period required for return to normal was 58 days, the peak icterus having been 180. There was no plateau, the peak was rapidly reached and recession of jaundice always started promptly.

HEMOGRAM. Study of the hemogram showed absence of anemia, normal total white blood count and a tendency toward reversal of the lymphocyte - neutrophil

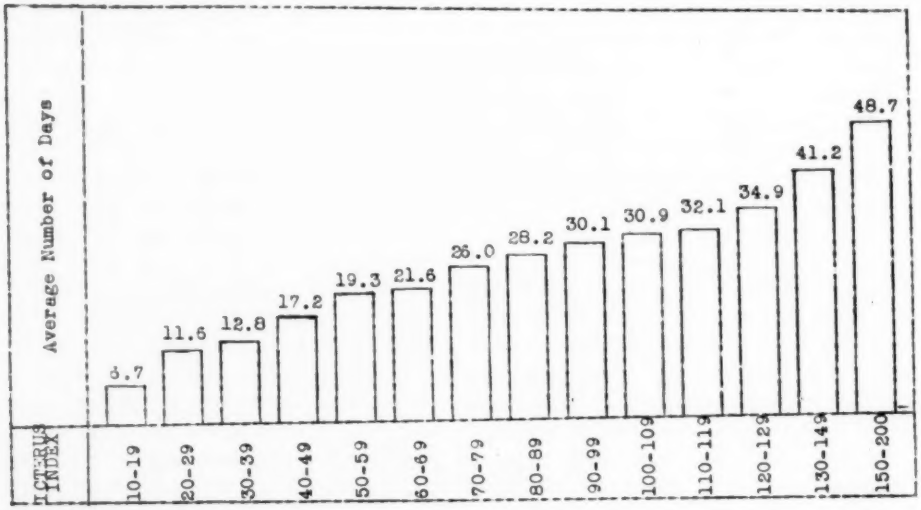

FIG. 2.—Relation between peak icterus and time required for icterus index to return to normal.

so-called "liver spots" during the 2nd and 3rd weeks of the disease. These were first seen as small (1 mm.) bright red areas on the arms, chest, and upper back which changed to brown in 24 to 48 hours. They became progressively darker during the following week, after which they remained relatively unchanged throughout hospitalization. No spider telangiectases were seen in the cases of acute hepatitis.

Laboratory Studies. ICTERUS INDEX. As indicated above, this test proved a rough measure of severity of the disease, and in general it was true that the longer the time required for return of icterus index to normal, the greater the duration

ratio (Table 5). A slight increase in eosinophils was noted in a considerable fraction of the group. This feature has not received emphasis previously. A check of patients with other diseases showed no abnormal concentration of eosinophils. Atypical lymphocytes' which have been said to occur frequently in this disease were noted in 15 of 50 blood smears studied with this in mind.

SERUM PROTEINS. The level of serum proteins (copper sulphate method) and protein partition* was studied in 100 patients. It was found that 81 cases with clinical and other laboratory evidence of persistent disease activity showed a level

* Albumin was determined by precipitation with 22½% sodium sulphate followed by digestion and "Nesslerization," globulin by the difference between the total protein and albumin.

of serum proteins above 7 gm. per 100 cc. and serum globulin above 2.5 gm. Only 3 patients, apparently well by all other criteria, however, showed this abnormality.

Sedimentation Rate. Sedimentation rate (Westergren) was normal during the early phase of the disease and if convalescence was complete, at the close of the period of hospitalization. On the other hand, during the 4th through the 8th week of the disease, if recovery was not complete, the sedimentation rate was moderately elevated (10 to 30 mm. per hour).

Table 5.—Hemogram in Infectious Hepatitis

Hemogram 295 Cases		Number of Cases	Per Cent
White blood cell concentration	3–6000 per c. mm.	30	10.3
	6–8000 per c. mm.	118	40.0
	8–10,000 per c. mm.	132	44.6
	10–13,000 per c. mm.	15	5.1
Lymphocytes, number	50–60 per 100 WBC	84	28.5
	40–50 per 100 WBC	96	32.6
	30–40 per 100 WBC	81	27.5
	20–30 per 100 WBC	34	11.4
Neutrophils, number	70–80 per 100 WBC	10	3.4
	60–70 per 100 WBC	29	9.8
	50–60 per 100 WBC	78	26.4
	40–50 per 100 WBC	99	33.6
	30–40 per 100 WBC	79	26.8
Monocytes, number	0–5 per 100 WBC	55	19.7
	5–10 per 100 WBC	171	57.9
	10–15 per 100 WBC	69	23.4
Eosinophils	0–3 per 100 WBC	124	41.3
	3–5 per 100 WBC	97	32.9
	5–10 per 100 WBC	74	25.8

Table 6.—Level of Serum Globulin (100 Cases)

Status	Number of Patients	More than 2.5 Gm. per 100 cc. Number	More than 2.5 Gm. per 100 cc. Per Cent	Less than 2.5 Gm. per 100 cc. Number	Less than 2.5 Gm. per 100 cc. Per Cent
With active disease	64	52	81.3	12	18.7
With apparent recovery	36	1	2.9	35	97.1

This proved a valuable criterion of fitness of a patient for reconditioning or discharge to duty, as well as often being the signal of a relapse.

Kahn. The Kahn examination was performed on the blood of 90 patients during the pre-icteric, early icteric and convalescent stages, as well as on the blood of patients in a relapse. In all cases the result was negative.

Urine. In the majority of patients, save for slight albuminuria during the pre-icteric and early icteric phase of the disease, and for the pigmentary changes, the urine was normal. In an occasional deeply jaundiced patient, the picture of so-called "bile nephrosis" appeared transiently, with a low specific gravity, moderate albuminuria and bile-stained casts. Moderate glycosuria was noted on one or two occasions. Glucose tolerance studies of those patients failed to reveal any abnormality.

The significant urinary changes were those related to the pigment disturbance in this disease. The first voided morning specimen was found to be reliable for measuring bilinuria and urobilinogenuria[8] and much less laborious than the 24-hour collection recommended by Watson.[14] It has been shown that, using a modification of the Sparkman procedure for urobilinogen determination, the presence of more than 2.4 mg. per 100 cc. of morning urine is abnormal.[8]

The diphasic curve of urobilinogen excretion, described by others[2] in this disease, was noted in this study, with a pre-icteric rise in urobilinogen, and a drop as the icterus begins to recede. When jaundice

was extreme and bilinuria massive, the urobilinogen at the time of peak icterus decreased to normal or subnormal levels, a situation simulating obstructive jaundice (Fig. 3). In the cases of hepatitis without jaundice, the diphasic curve is not seen, and unless a relapse occurs, there is a continuous decrease in urobilinogen level from time of entry into the hospital. Abnormal amounts of urobilinogen in the urine were not only often the first laboratory evidence of early hepatitis and incipient relapse in a convalescent, but also frequently served as an important laboratory aid confirming the diagnosis of hepatitis without jaundice.

The urine was examined for the presence of bile salts in 25 cases with deep jaundice, pruritus and bradycardia. In all but 2 cases the test was positive.

Although no attempt was made to assay the pigment content of the feces, it was noted that in 61 cases, or over 20% of the group, light stools were noted at the time of deepest icterus.

Liver Function Tests. The result of the *cephalin-cholesterol flocculation test* was studied in the first 75 cases, and although the test was positive in all cases, it was discarded as a means of following the patients when it was found that the blood of many apparently recovered cases, as well as of many apparently normal individuals, also gave positive readings. Whether this was due to lack of familiarity with the technique of the determination or to too highly sensitive a reagent cannot be stated.

Hippuric acid excretion after administration of oral sodium benzoate was tested in the same number of patients, but, like the cephalin flocculation test, proved of little value in this study. Many patients with obvious liver damage by other criteria showed normal hippuric acid excretion, while some who were apparently recovered continued to show apparent impaired ability to convert benzoic to hippuric acid.

Because of lack of materials and equipment, the dye excretion tests, serum phosphatase determination, cholesterol-cholesterol ester ratio and the prothrombin time determination were not attempted.

Miscellaneous. To insure the fact that no cases of Weil's disease were being overlooked, 20 patients most closely simulating leptospirosis clinically were subjected to a study of the urine for the organisms and the serum for the specific agglutinins. The results were uniformly negative. Similarly, examination of the sera of 20 patients, whose blood showed a reversal of the neutrophil-lymphocyte ratio, failed to reveal the presence of the heterophil agglutinin seen in infectious mononucleosis.

Comment. The general clinical picture noted in this study is similar to that usually described. Ocular pain, however, was a more frequent component of the headache than was noted in Cameron's[2] series. Worthy of note in the present study were the distinct categories of onset, and the realization that influenza or respiratory disease may be simulated in the pre-icteric period. The relatively high incidence of itching and bradycardia in this series, while in contrast with the rarity of these symptoms in the group studied by Hayman and Reed,[4] parallels the observations of Lucké[5] and Cameron.[2] In conformity with this observation was the presence of bile salts in the urine of patients showing such symptoms.

Urobilinogenuria has been shown to be one of the most sensitive indices of liver function.[10,11,14] A diphasic curve of urobilinogen excretion, with one rise in the pre-icteric period and another with decline of icterus has been reported by others[2] and noted in this series. Elevated urobilinogen levels in the urine serve as an extremely helpful clue for diagnosis before the appearance of icterus or in cases of hepatitis without jaundice. During the course of the disease, frequent determinations of the level help evaluate the progress of the patient, and when a rise in level occurs after previous return to normal, it serves to herald a relapse.

The observation[1,15] that the sedimenta-

tion rate early in this disease is low or only slightly elevated, also noted in this series, is from the negative standpoint, a helpful diagnostic feature. In a patient with equivocal evidence of early hepatitis, the presence of a sedimentation rate above 15 mm. in 1 hour, renders the diagnosis unlikely or suggests the presence of some complicating disease. Paradoxically enough, during convalescence the sedimentation rate, when elevated, shows the presence of continued or renewed activity of the inflammatory process in the liver.

No "false-positive" serological tests for syphilis were noted. The Kahn test, performed at all stages of the disease, was uniformly negative.

The concept of hepatitis without jaundice has recently received emphasis.[1,3,6,12,13] The proportion of cases of hepatitis which do not show jaundice reported by Barker[1] is far greater than that observed in the present study. Whether this apparent difference in incidence actually represents a difference between the two epidemics, or merely a difference in diagnostic criteria cannot be decided at this time. The diagnosis in this study was based on the occurrence of symptoms, physical findings and laboratory changes differing only in degree from those seen in cases of hepatitis with jaundice. Of significance was the occurrence of malaise, anorexia, epigastric fulness or distress, pain in the right upper quadrant or back, and tenderness in these areas with or without a palpably enlarged liver. The findings of increased urobilinogen levels in the urine and serum globulin in the blood confirmed the diagnosis.

Pre-icteric hepatitis and hepatitis without jaundice may present an identical picture and it is often impossible to predict whether jaundice will occur. The importance of the recognition of hepatitis without jaundice, when it occurs, lies in its potentiality of relapse and chronicity analogous to that of the cases of jaundice.

The criteria of recovery, as outlined by Barker[1] and applied in this study, are worthy of emphasis. Until the icterus index has returned to normal, disease is still present. Attempts to start patients on physical activity before the icterus had been normal for at least 2 weeks almost invariably lead to relapse. Similarly, instituting physical exercise in a patient whose urobilinogen level is still above 2.0 mg. per 100 cc. of morning urine or whose sedimentation rate is above 10 mm. in 1 hour will usually lead to relapse. Of equal importance, although usually parallel with these laboratory features, are the clinical evidences of disease activity as outlined in the body of this paper. Finally, the acid test of the fitness of a patient for discharge from the hospital is his ability to tolerate physical exertion without the occurrence of symptoms, signs or laboratory evidence of a relapse.

It has been recommended that the treatment accorded hepatitis be a regimen of rest and rigid diet.[1] Bed rest during the acute phase of the disease and during early convalescence is of paramount importance; for inadequate bed rest and too early return to activity lead to relapses and to chronic hepatitis.

Recent studies[9] have shown the importance to the liver of adequate protein intake. Since there was no control group, with respect to diet, used in the present study, evaluation of the efficacy of the high-protein, low-fat regimen is difficult. It was, however, noted that patients transferred from other wards, where they had been receiving a "regular diet", to the hepatitis section, experienced an increase in appetite and an amelioration of symptoms after several days of the "special" diet. Furthermore, the absence of deaths in this series may be significant. Since the mortality rate in this disease varies from 0.2% to 0.4%,[5] it is difficult to predict whether in a series of the size studied here any deaths could have been expected. Nevertheless, several patients presented clinical and laboratory features similar to those considered prognostic of a fatal termination. Whether the survival of these patients was due to the high dietary protein regimen liberally supplemented by plasma cannot be determined.

The following case exemplified the insidious type of onset, the severity which this disease occasionally manifests, indications for the use of plasma, and the occasional simulation, from a laboratory standpoint, of "obstructive jaundice" (Fig. 3). The diphasic curve of urobilinogen excretion is also illustrated.

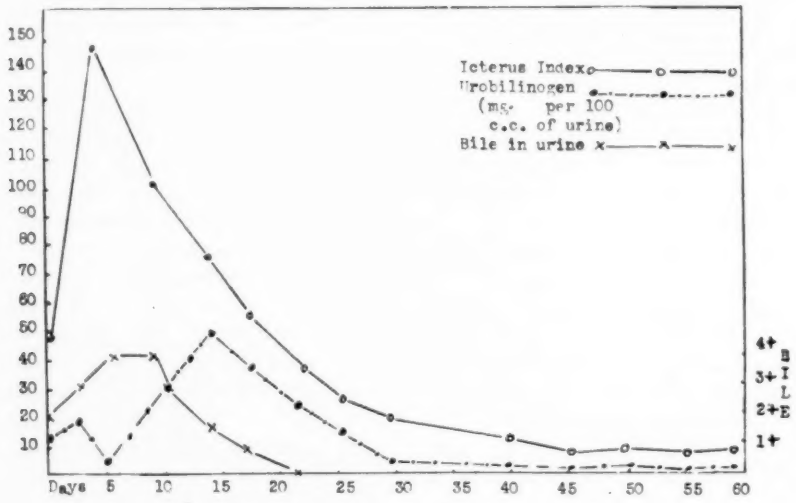

FIG. 3.—Case 105. A. L.

Case Reports. CASE 105. A. L., aged 24, was admitted to the hospital on March 21, 1945, with a history of gradual onset, during the preceding 12 days, of malaise, anorexia, and heavy, leaden pain in the epigastrium. Eight days before entry he noted dark urine, and, on the following day, he became constipated. On March 19th, he noted light stools, his skin began to itch and friends noted that he was turning yellow. Six weeks prior to entry he had had severe diarrhea for 1 week.

On entry he was moderately jaundiced, had enlargement of cervical lymph glands, and the liver edge, which was moderately tender, was 4 cm. below the right costal margin. Temperature was 98.2° F., pulse 52, and respirations 16.

The hemoglobin value and red blood cell count were normal (14.0 gm. and 4,800,000). There were 7,200 white blood cells per c.mm., of which 38% were neutrophils, 52% lymphocytes, 6% monocytes and 4% eosinophils. The serum globulin level was 3.1 gm. per 100 cc. The icterus index on entry was 48, the blood Kahn test negative and the sedimentation rate 6 mm. in 1 hour. Examination of the urine showed a specific gravity of 1.011, a "two plus" albuminuria, no sugar, and frequent bile-stained hyaline and granular casts. Bile was present and there were 15 mg. of urobilinogen per 100 cc. of urine. Bile salts were present in the urine.

Course. The jaundice deepened rapidly, the liver descended to the umbilicus and anorexia remained moderate. On the 9th hospital day, anorexia became absolute and the patient became drowsy, irritable and developed nausea and vomiting. From the 9th through the 14th day, he was given infusions of 500 cc. of plasma daily. By the 14th day he was eating well and icterus was slowly receding. Improvement thereafter was slow but continuous. At the end of 60 days, because the liver was still enlarged and tender, and bloating, malaise and listlessness still present, he was evacuated to the Zone of the Interior.

The next case demonstrates the course of a mild hepatitis with jaundice. He was admitted to the hospital when jaundice was already receding, the first peak of urobilinogen was missed and the diphasic curve is not apparent (Fig. 4).

Case 56. R. S., aged 26, entered the hospital on March 13, 1945, complaining of malaise and anorexia for 8 days. Before he lost his appetite, however, he had felt chilly and feverish for 1 day. Five days prior to entry he developed a dull aching in the epigastrium and a "tired" feeling in the back. Two days before admission the urine became dark. Early in February he had suffered a mild bout of diarrhea.

On admission he was moderately icteric. There was generalized enlargement of the lymph glands and a liver edge was felt just below the rib margin. Temperature was 98.8° F., pulse 58 and respirations 14.

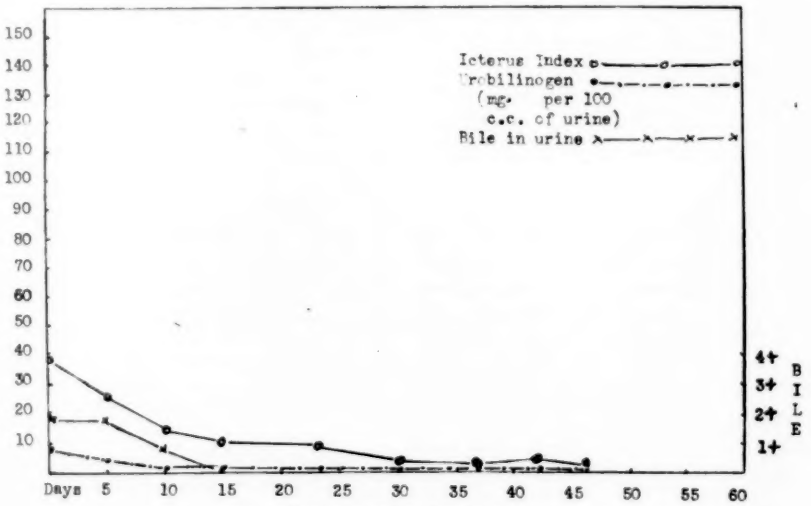

Fig. 4.—Case 56. R. S.

In the urine there was bile and 12.0 mg. of urobilinogen per 100 cc. Sedimentation rate was 11 mm. in 1 hour, and the Kahn test negative. There were 14.8 gm. of hemoglobin per 100 cc., 4,900,000 red cells and 6,400 white cells per c. mm. of blood.

Course. Jaundice gradually receded and by the end of the 3rd week had completely cleared. He began to eat well, on the 3rd hospital day his abdominal pain rapidly diminished and by the end of the 2nd week in the hospital had completely disappeared. Save for occasional bloating during the 3rd and 4th week, he had no further adverse symptoms. On the 36th hospital day, 2 weeks after return of his icterus index to normal, he was started on the reconditioning program. At this time urine and sedimentation rate were normal and liver edge was no longer palpable. After 10 days of reconditioning, when again sedimentation and urine were normal he was discharged to full duty.

The following case shows the course of laboratory findings in a patient who developed relapse with jaundice. Although most relapses seemed the result of excess or premature physical activity or intercurrent infection, this case relapsed in spite of absence of these factors (Fig. 5).

Case 114. J. J., 25 years old, was admitted to the hospital on March 18, 1945, with a history of malaise, anorexia, nausea, abdominal pain and dark urine for 10 days, and jaundice for 3 days. He had had a severe bout of diarrhea during the 3rd week in February. On admission he was moderately jaundiced, showed generalized lymph gland enlargement and a tender liver 3 cm. below the costal margin. Icterus index on entry was 56. There was marked bilinuria and urobilinogenuria.

Course. During the following 3 weeks jaundice, anorexia and abdominal pain receded gradually. On the 24th day of hospitalization, in spite of rigid adherence to the prescribed regimen of rest and diet, there was a return of epigastric distress and

loss of appetite. Urine showed increased urobilinogenuria, and icterus again began to deepen. Icterus index rose to a peak of 48 and then again began to recede. At the end of 60 days of hospitalization, because he was still complaining of epigastric fulness and bloating, and the liver was still tender and enlarged, he was evacuated to the United States.

recovered. The significance of even slightly abnormal urobilinogenuria as a criterion of incomplete recovery is well illustrated (Fig. 6).

CASE 123. R. A., aged 20, entered the hospital on March 16, 1945. Five days prior to entry he developed moderate fever, malaise, anorexia, nausea and dull leaden

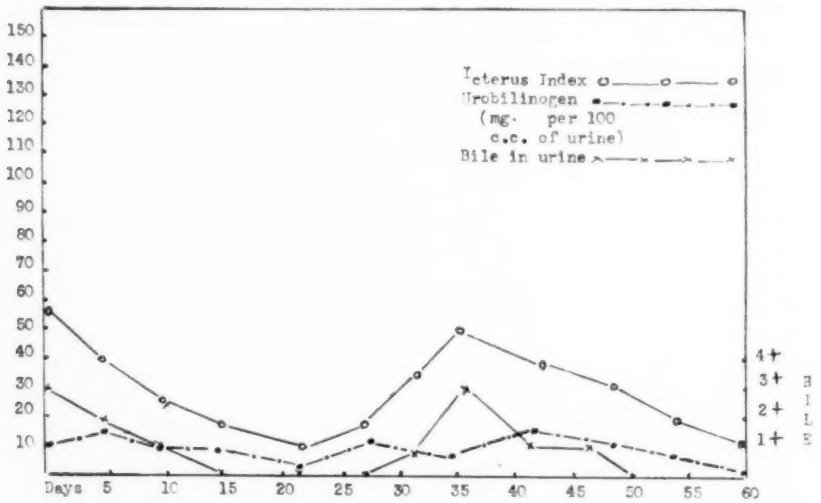

FIG. 5.—Case 114. J. J.

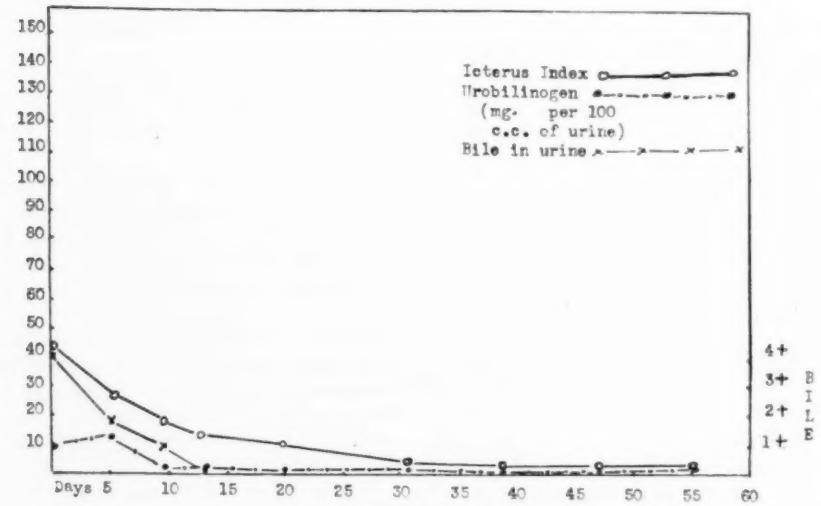

FIG. 6.—Case 123. R. A.

The next case demonstrates relapse without jaundice in a patient discharged from the hospital before he had completely

epigastric pain. On the following day he developed dark urine and on the day of admission skin jaundice was noted. On

admission he was moderately jaundiced. The liver was enlarged and tender. Icterus index was 44 on entry.

Icterus receded gradually and had disappeared by the 20th day. Urobilinogenuria dropped to normal levels by the end of the 4th week. He continued to have full epigastric distress and bloating and the tenderness persisted until the end of the 6th week in the hospital. At that time, with normal urine and sedimentation rate, he was subjected to a ten-day period of reconditioning. On the 56th hospital day, sedimentation was 9 mm. in 1 hour and the urine urobilinogen level was slightly above normal, and he was returned to duty. Ten days later he was readmitted to the hospital, having suffered a recurrence of right upper quadrant pain and anorexia 4 days previously which had grown progressively more severe. On entry he was listless, pallid (when discharged from the hospital, color had been good), the liver was again enlarged and tender. There were 6 mg. of urobilinogen per 100 cc., the sedimentation rate was 18 mm. in 1 hour, and there were 3.3 gm. of globulin per 100 cc. of serum. Although the urobilinogen level of the urine dropped to normal levels after 2 weeks of bed rest and "special diet" persistence of malaise, epigastric distress and tenderness as well as a continued high serum globulin necessitated evacuation to the United States.

The following case illustrates hepatitis without jaundice. Its clinical similarity to the forms with jaundice is evident.

Case 125. R. S., aged 19, was a member of a unit with a high incidence of infectious hepatitis. On March 19, 1945, he was admitted to the hospital with a history of chills and fever for 2 days, pain in the right upper abdominal quadrant for 1 day. Five weeks previously he had had diarrhea for 6 days. On entry there was generalized enlargement of the lymph glands, tenderness in the epigastrium and the liver edge was felt 2 cm. below the costal margin. Temperature was 99.2° F., pulse 68, respiration 16. Hemoglobin and red blood cell values were normal. White blood cell count was 6,100, with 51% lymphocytes, 38% neutrophils, 9% monocytes and 2% eosinophils. Serum globulin level was 2.9 gm. per 100 cc., icterus index 9 units and sedimentation rate 12 mm. in 1 hour. In the urine there was a trace of albumin, 3.8 mg. of urobilinogen per 100 cc., but no bile nor other abnormalities.

Abdominal distress, moderate anorexia, size and tenderness of the liver and urobilinogenuria slowly receded. At the end of 2 weeks, urobilinogen levels were normal and at the end of 3 weeks all symptoms had disappeared. After 4 weeks in the hospital the liver was no longer palpably enlarged and there was no abdominal tenderness. He was given 10 days of physical exercise (reconditioning). At the end of this period with sedimentation rate and urobilinogen level normal, he was returned to duty.

The next case demonstrates the ability of a case of hepatitis without jaundice to develop icterus in a relapse. This potentiality again shows the identity of the nonjaundiced with those showing icterus (Fig. 7).

Case 128. W. Y., aged 23, entered the hospital on March 28, 1945, with a history of fever and chills for 3 days, anorexia, nausea and abdominal pain for 2 days. On admission he was not jaundiced, had cervical lymphadenopathy, and a tender liver edge 3 cm. below the right costal margin. Temperature was 101° F., pulse 64, respirations 18. Hemoglobin and red blood cell count were normal. There were 5,400 white blood cells per c. mm. of blood, of which 46% were lymphocytes, 49% neutrophils, and 5% monocytes. Serum protein level was 7.3 gm. per 100 cc. of which globulin constituted 2.6 gm. The only urinary abnormality was the presence of 4.5 mg. of urobilinogen per 100 cc.

Symptoms and urobilinogen excretion gradually receded. At the end of 3 weeks he was feeling completely well and the urobilinogen level was normal. During the 4th week, although not authorized to do so, he began to indulge in physical activity. On the 26th hospital day he suffered a recurrence of anorexia and epigastric pain. On the following day increased amounts of urobilinogen were noted in the urine. Two days later clinical jaundice was noted. A peak icterus index of 48 units was achieved. Thereafter there was gradual recession of the icterus and symptoms. At the end of 60 days of hospitalization, anorexia and abdom-

inal pain persisted and he was evacuated to the United States.

Summary and Conclusion. The group was classified in terms of disease patterns seen depending on the presence or absence of jaundice, occurrence of relapses, and severity. The incubation period was estimated to fall within the accepted 3- to 6-week range. Onset was categorized on the basis of the insidiousness or rapidity of the symptom evolution, and presence or prominence of systemic and respiratory symptoms. Frequency of symptoms was shown with anorexia, dark urine, malaise, nausea, and abdominal pain most common. Jaundice, tender hepatomegaly, adenopathy and occasional splenomegaly were the significant signs.

Duration of signs and symptoms was rarely less than 5 weeks and many patients had residual disease after 8 weeks. Criteria for recovery have been outlined, and the necessity for rigid conformity to those criteria emphasized. The possibility and characteristics of relapses were discussed.

Although no deaths occurred, there were 6 cases which showed a clinical picture said to herald a fatal outcome. Most complications noted were mild. Gingivitis, skin petechiae, melena, epistaxis, and "liver spots" occurred. One patient developed a typical Guillain-Barre syndrome. A number of cases showed transient behavior changes.

The course of icterus and urobilinogenuria were described. The typical hemogram with absence of anemia, normal white blood count, but with a tendency to reversal of the lymphocyte-neutrophil ratio, and slight increase in eosinophils was described. The diagnostic and prognostic significance of an elevated serum globulin has been shown. The presence of bile salts in the urine of patients with deep jaundice, bradycardia, and itching was noted.

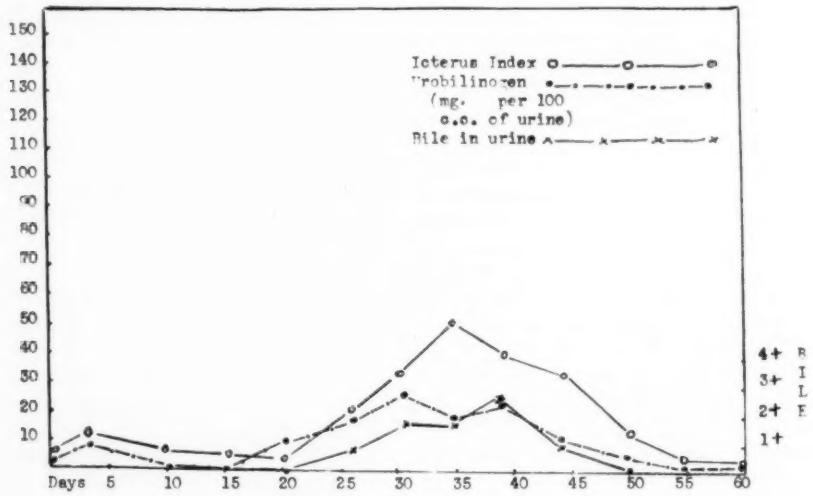

FIG. 7.—Case 128. W. Y.

This report is another illustration of the prevalence of infectious hepatitis and its importance as a disabling disease of military personnel. The treatment followed has a firm theoretical basis and growing clinical supporting evidence. It is hoped that a realization of the need for adherence to this regimen and for careful use of the criteria of recovery will aid in preventing the sequelae and residua of hepatitis. Similarly the recognition and treatment of cases of hepatitis without jaundice are highly important in the prevention of chronic hepatitis.

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LIVER DYSFUNCTION IN RHEUMATIC HEART DISEASE

PRELIMINARY REPORT

By R. W. Kissane, M.D.
R. S. Fidler, M.D.
AND
Thomas E. Clark, M.D.
COLUMBUS, OHIO

(From the Medical and Pathological Departments of Ohio State University and White Cross Hospital, Columbis, Ohio)

There has been considerable doubt as to just how much liver damage occurs as the result of heart disease, because passive congestion of the liver develops rather suddenly with the beginning of heart failure and frequently disappears just as quickly with the return of a normal circulation. The pathology of this condition was described by Fishberg[3] as an engorgement of the central vein and adjacent capillaries, with the liver cells between the vessels soon becoming affected. These changes may advance to the degree that there is atrophy and replacement of the liver cells by fibrosis, which would make it reasonable to suspect that liver dysfunction occurs. This has been shown to be true not only in heart failure [2,6] but Bingen and Stolte[1] found that a large percentage of a group of patients with acute and chronic rheumatic polyarthritis exhibited deviations from the normal in various liver tests. In order to determine whether liver dysfunction occurs only at the time of heart failure or whether it is a gradually developing process, a series of 154 cases of rheumatic heart disease were studied, because in this type there exists a more easily measured period of time between the initial cardiac damage and heart failure. There was no special selection made in this entire group which was obtained by taking all cases as they presented themselves for examination. However, from this group 17 cases were eliminated because either by history or clinical evidence there was the slightest possibility of liver or gall bladder disease. All cases having any congenital cardiac lesion were also eliminated. The remaining 137 cases were given the cephalin-cholesterol flocculation test as described by Hanger.[4,5] We considered this test ideal because it has been shown that a cephalin-cholesterol emulsion was flocculated by serum from patients with active disturbances of the liver parenchyma and parallels the severity of the dysfunction. It may therefore be employed to estimate the degree or persistence of an active liver process. The test was always performed by the same technician and the results checked by one of us and plus-minus reactions were considered as negative.

Results. In the series of 137 cases of rheumatic heart disease there were 97 positive cephalin-cholesterol flocculation reactions (70%). The group was further subdivided into those cases that were or had been in heart failure at some time. There were 18 such cases with 15 positive reactions (84%). There were 17 cases of auricular fibrillation of which 14 showed positive reactions (82%) and in 5 cases of interventricular block all were positive (100%). Further inspection of this group revealed 4 cases of heart failure without any disturbance of rhythm or conduction of which 3 (75%) showed positive reactions. Of the cases of auricular fibrillation, all but 4 either were or had been in heart failure and of these 3 (75%) showed positive reactions. One of the cases of interventricular block also was in heart failure. The balance of the cases, 111 in number, were considered as of first and second degree cardiac function, and of these there were 75 showing a positive

reaction (67%). Grouped according to the vascular lesion present, they revealed positive cephalin-cholesterol flocculation reactions in 41 (77%) of 53 cases of mitral stenosis, 30 (64%) of 47 cases of mitral insufficiency, 24 (75%) of 32 cases of mitral stenosis and insufficiency, and 5 (55%) of 9 cases of aortic insufficiency. The remainder of the cases, few in number, had combined valvular lesions and therefore were not classified.

Table 2. It appears that after rheumatic heart disease has existed 1 year a positive cephalin-cholesterol flocculation reaction occurs and the number of years duration of the disease does not influence the percentage of positive reactions nor change the percentage from that of the entire group. The same close relationship of percentages were observed between the children and young adult cases under 20 years of age to the entire series when

TABLE 1.—AGE GROUPS AND CEPHALIN-CHOLESTROL FLOCCULATION TESTS OF 142 CASES OF RHEUMATIC HEART DISEASE

Years	Cephalin-Cholesterol Flocculation			Percentage
	Positive	Negative	Plus-minus	Positives
0–10	2	1	6	22
11–20	17	4	5	65
21–30	16	3	0	83
31–40	21	9	1	67
41–50	21	7	0	75
51–60	15	6	0	71
61–70	6	1	1	75

Plus-minus reactions were considered as negative.

TABLE 2.—APPROXIMATE DURATION OF RHEUMATIC HEART DISEASE AND CEPHALIN-CHOLESTEROL FLOCCULATION TESTS IN 128 CASES

Years	Cephalin-Cholesterol Flocculation			Percentage
	Positive	Negative	Plus-minus	Positives
0–1	0	1	3	0
1–2	7	3	0	70
2–4	4	0	1	80
4–6	3	3	1	43
6–10	10	0	1	90
10–15	9	3	0	75
15–20	22	4	0	84
20–25	10	3	0	76
25–30	9	4	1	64
30–35	9	0	0	100
35–up	13	4	0	76

Duration estimated from etiological attack or when heart disease was first recognized.
Plus-minus reactions were considered as negative.

The age range in the entire series of cases of rheumatic heart disease was from 7 to 67 years. In order to determine whether or not aging had any relationship to this phenomenon the cases were subdivided into decades as shown in Table 1. This, however, does not give any information as to how long rheumatic heart disease must be present before positive cephalin-cholesterol flocculation reactions are obtained. There were 128 cases in which it could be ascertained with a relative degree of certainty the number of years this disease had been present and these were divided into time periods as shown in

they were subdivided according to the valvular lesion present. The positive reactions were 5 (45%) in 11 cases of mitral insufficiency, 6 (86%) of 7 cases of mitral stenosis and insufficiency, and 4 (80%) of 5 cases of mitral stenosis. None of these cases was in heart failure nor had auricular fibrillation; however, in 2 cases with auricular fibrillation there were positive reactions.

The group of 97 cases were investigated as to whether there was any correlation between the degree of cephalin-cholesterol-flocculation-positive reactions and the severity of the rheumatic heart disease.

The 22 positive reactors with auricular fibrillation, heart failure or interventricular block were divided as follows; 13 were plus 1 or 2, and 9 plus 3 or 4, and the 75 positives in cases of slightly to moderately advanced rheumatic heart disease were 39 plus 1 or 2, and 36 plus 3 or 4. There did not appear to be any relationship between the degree of positive reaction and the degree of heart disease.

Summary. 1. The cephalin-cholesterol flocculation reaction was found positive in 72% of 136 cases of rheumatic heart disease.

2. The cephalin-cholesterol flocculation reaction was positive in 89% of the cases with heart failure, 82% of the cases with auricular fibrillation and 100% of those with interventricular block.

3. The cephalin-cholesterol flocculation reaction was positive in 69% of 110 cases of rheumatic heart disease considered as of first or second degree cardiac function.

4. Neither the valvular lesion, age of the patient nor the length of time rheumatic heart disease existed seemed to effect any variation from the percentage of positives of cephalin-cholesterol flocculation reactions in the entire group.

5. There was no correlation found between the degree of positive cephalin-cholesterol flocculation reaction and the degree of functional severity of rheumatic heart disease.

The authors wish to thank 1st Lt. H. V. Bieghler of Strouthers, Ohio, for his assistance in preparing this report.

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THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA WITH ORAL AND INTRAMUSCULAR PENICILLIN

By Harry F. Dowling, M.D.
Georgine Rotman-Kavka, M.D.
Hugh H. Hussey, M.D.
and
Harold L. Hirsh, M.D.

(From the Health Department, Washington, D. C., George Washington Medical Division, Gallinger Municipal Hospital, and the Department of Medicine, George Washington University School of Medicine)

The value of penicillin in the treatment of pneumococcic pneumonia has been amply demonstrated. Numerous reports[1,3,7,8,10,13] attest to its effectiveness when it is administered by the intramuscular route. The results in a relatively small number of patients with this disease who have been treated with this antibiotic by oral administration have been good.[2,6,11] Since the oral route is more desirable for the patient and since it does not require hospitalization or special nursing care, it would be the method of choice in most instances if the physician could be certain that the results would be as good as when parenteral methods were used. In an effort to answer this latter question we have treated comparable groups of patients with penicillin by the intramuscular and oral routes.

Method. Blood for culture and sputum for pneumococcus typing were obtained from all patients admitted to the medical wards of the Gallinger Municipal Hospital who were diagnosed as having pneumonia. The patients were then given either 15,000 units of penicillin intramuscularly every 3 hours or 75,000 units by mouth at the same intervals. The two routes of administration were used without any selection of cases except that the oral preparation was employed when it was available and the intramuscular route at other times. One patient who was scheduled to receive penicillin orally was given the drug intramuscularly instead, because he was comatose on admission. His case has been placed in the oral group in our calculations.

The intramuscular preparations used were various lots of commercial penicillin G (in 73 patients), crystalline penicillin G* (in 34 patients), and penicillin X† (in 3 patients). The oral doses were usually given in the form of tablets containing 25,000 units of sodium penicillin buffered with calcium carbonate.† Penicillin treatment was continued until the temperature had fallen and remained at or below 100° F. for 2 to 4 days.

Results. Since no significant differences were observed in the results obtained with the use of commercial penicillin G, crystalline penicillin G, and penicillin X intramuscularly, the patients treated with these preparations have been placed in one group for the purposes of this paper. A comparison of the therapeutic effects of these preparations in various diseases including pneumococcic pneumonia is being published elsewhere.[12] It will be seen from Tables 1 and 2 that the groups of patients treated by the two routes were comparable with respect to the types of pneumococci causing the disease and were essentially similar in respect to age distribution. The incidence of bacteremia was somewhat higher in the group of patients who received penicillin intramuscularly and there was a slightly larger proportion of patients

* Supplied by Merck and Company, Rahway, N. J.
† Supplied by the Lederle Laboratories Incorporated, Pearl River, N. Y.

above the age of 50 years in the intramuscular-treatment group.

There were 59 patients in the oral-treatment group, of whom 3 (5.1%) died. Among the 190 patients in the intramuscular-treatment group, there were 9 deaths (8.3%). This difference is not considered significant, in view of the fact that there was a greater proportion of patients in the older age-groups in the intramuscular-treatment group. Furthermore, there were 6 patients with bacteremia treated with oral penicillin, 2 of whom died, and 18 bacteremic patients given intramuscular penicillin among whom only 3 died.

the first day is almost identical among the patients treated with oral and the patients treated with intramuscular penicillin (57% and 59% respectively). By the end of the 2nd day after treatment was started, the figures for the 2 groups were 86 and 85% for the oral-treatment and intramuscular-treatment groups, respectively. Thus it appears that there was very little difference in the rate at which the temperature fell, regardless of whether the penicillin was given by mouth or by intramuscular injection. This similarity is illustrated by Figures 1 and 2 which portray representative temperature charts from patients

TABLE 1.—RESULTS OF TREATMENT WITH PENICILLIN ORALLY AND INTRAMUSCULARLY, ARRANGED ACCORDING TO TYPE OF PNEUMOCOCCUS

Type of Pneumococcus	Oral Penicillin				Intramuscular Penicillin			
	All Cases		Bacteremic Cases		All Cases		Bacteremic Cases	
	Number	Died	Number	Died	Number	Died	Number	Died
1	7	1	2	1	12	1	6	1
2	8	0	1	0	12	0	1	0
3	9	0	0	0	13	3	3	2
4	3	0	1	0	6	0	2	0
5	..	..	..	..	2	0	1	0
6	5*	1*	0	0	4	0	0	0
7	9	0	1	0	18	0	3	0
8	..	..	..	..	8	1	0	0
Other types	14	1	1	1	27	2	2	0
No type obtained	4	0	0	0	6	1	0	0
Total	59	3 (5.1%)	6	2 (33.3%)	109	9 (8.3%)	18	3 (16.7%)

* One patient received intramuscular penicillin because he was in coma.

TABLE 2.—RESULTS OF TREATMENT WITH PENICILLIN ORALLY AND INTRAMUSCULARLY, ARRANGED ACCORDING TO AGE OF PATIENTS

	Oral Penicillin		Intramuscular Penicillin	
	Number	Died	Number	Died
12–20	5	0	10	0
21–30	14	0	24	0
31–40	20	2	28	1
41–50	8	0	21	1
51–60	8	1	9	2
61–70	3	0	7	1
over 70	1	0	10	4
Total	59	3	109	9

One method which we[4,5] have found useful in comparing the results obtained in patients with pneumococcic pneumonia treated by various drugs is to determine the rapidity with which the temperature falls and remains below 101° F. among the patients who have recovered. From Table 3 it will be seen that the percentage of patients who experienced a crisis within

receiving this antibiotic by the 2 methods of administration.

In addition to the case fatality rate and the rate of temperature fall, another important method of judging the value of a drug in pneumococcic pneumonia is its effectiveness in preventing complications. Six of the patients treated with penicillin orally, and 16 of those who received it

intramuscularly, developed complications. None of these complications were serious nor were they the cause of death in any instance. One patient was classified as having developed empyema because 30 cc. of cloudy fluid were removed from his pleural cavity on the 4th day of treatment. Although the fluid was purulent, direct smear and culture revealed no organisms. At the time of the thoracentesis, an attempt was made to inject 50,000 units of penicillin into the pleural space but this could not be done, since the cavity was filled by the quantity of solution which contained 5,000 units. Since no further signs or roentgenologic evidences of pleural fluid appeared, additional thoracenteses were not performed. Subsequent recovery was without incident.

Discussion. When similar doses of penicillin are administered orally and intramuscularly the blood concentrations obtained with the former method are not as high as those obtained following intramuscular injections. McDermott and his co-workers[9] have shown that the chief reason for this fact is that only a small portion of the penicillin is absorbed from the gastrointestinal tract.

It has been recommended that oral

TABLE 3.—RAPIDITY OF CRISIS IN RECOVERED PATIENTS

	Oral Penicillin		Intramuscular Penicillin	
	Number of Patients	Per cent of Recovered Patients	Number of Patients	Per cent of Recovered Patients
Temperature 101° F. or below, within:				
0 to 23 hours	30	57	59	59
24 to 47 hours	16	29	26	26
48 hours and over	8	14	15	15
All Recovered Patients	56	100	100	100

TABLE 4.—COMPLICATIONS OF PNEUMONIA

Complication	Patients Receiving Oral Penicillin	Patients Receiving Intramuscular Penicillin
Pleural Effusion	1	2
Empyema	1	0
Delayed Resolution	2	9
Spread into Another Lobe	0	2
Relapse	1	2
Otitis Media	1	1

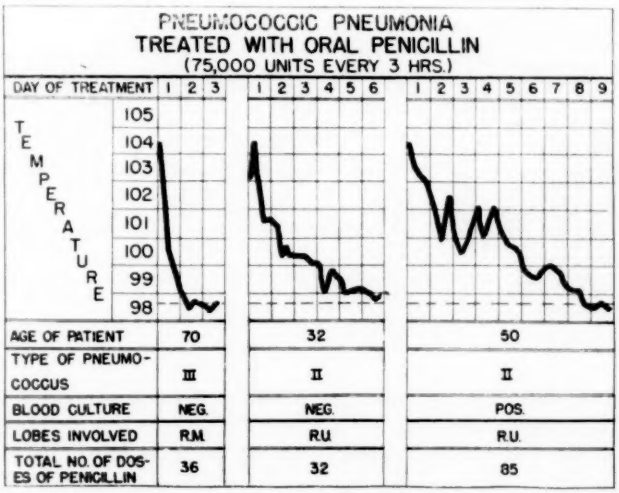

FIG. 1.

penicillin should be given in doses 3 to 5 times as great as those employed by the intramuscular route because of this irregular absorption. Bunn and his associates[2] treated 45 patients with pneumococcic pneumonia by the oral administration of 200,000 units initially followed by 50,000 units at 2-hour intervals. One patient in this group died and 1 developed empyema. Finland and his co-workers[2] gave 150,000 to 300,000 units initially and 90,000 or 100,000 units every 2 hours to 7 patients, all of whom recovered. Ross and his associates[2] observed recovery in the case of 2 children whom they treated with 100,000 units at 3-hour intervals.

ative. Oral therapy is preferable when it is not feasible to give multiple injections (as in the treatment of patients at home) or when the patients object to the frequent injections. Administration of penicillin by injections in beeswax and oil may be said to occupy a middle ground between the other 2 methods. This preparation need not be given as often (every 12 or 24 hours) but is more expensive than the products given by multiple injections, as expensive, in fact, as giving larger doses orally.

The results obtained in pneumococcic pneumonia with the use of penicillin by either method were excellent. The total

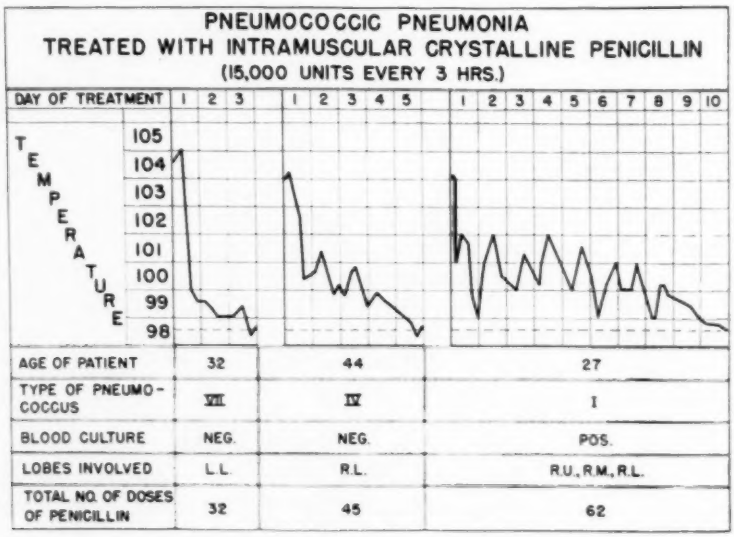

FIG. 2.

We decided to administer to our patients either 15,000 units intramuscularly or a dose 5 times as great, 75,000 units, orally. The results, as judged by the case-fatality rate, rapidity of temperature-fall and incidence of complications, were similar in the 2 groups. As a result of these observations, the indications as to the route of administration of penicillin in patients with pneumococcic pneumonia may be stated as follows: intramuscular therapy is preferable when cost is a major factor or when the patient is comatose or uncooperative. Oral therapy is preferable when it is not feasible to give multiple injections (as in the treatment of patients at home) or when the patients object to the frequent injections. Administration of penicillin by injections in beeswax and oil may be said to occupy a middle ground between the other 2 methods. This preparation need not be given as often (every 12 or 24 hours) but is more expensive than the products given by multiple injections, as expensive, in fact, as giving larger doses orally.

The results obtained in pneumococcic pneumonia with the use of penicillin by either method were excellent. The total number of patients treated with penicillin was 168 and the total number of deaths 12, giving a case fatality rate of 7.1 %.

We would like to stress 2 additional facts about the oral administration of penicillin: First, it seems best in view of the evidence available at present, that the oral route should not be used for the treatment of the more severe infections, such as bacterial endocarditis, staphylococcic bacteremia and pneumococcic meningitis. Second, when penicillin is administered orally it should always be given in large

doses, preferably 5 times as large as those which would be given intramuscularly in the treatment of the same infections.

Summary and Conclusions. 1. Among 168 patients given penicillin for pneumococcic pneumonia 12 (7.1%) died. Fifty-nine of these were selected (upon the basis of the availability of the oral preparation) to receive penicillin by mouth in doses of 75,000 units every 3 hours, and of these 3 (5.1%) died. Another group of 109 patients were given penicillin by intramuscular injections of 15,000 units every 3 hours. Among these 8 (7.4%) died. The rapidity of crisis and the incidence of complications were approximately the same among the patients in the oral-treatment and intramuscular-treatment groups.

2. It is concluded that patients with pneumococcic pneumonia may be treated with penicillin administered orally if large enough doses are given. Doses of 75,000 units given every 3 hours until the temperature has fallen and has remained below 100° F. for 48 to 96 hours are satisfactory for routine treatment.

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2111 Bancroft Place, N. W.
Washington, D. C.

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SOME PHARMACOLOGICAL AND CLINICAL EXPERIENCES WITH DIMETHYLAMINOETHYL BENZHYDRYL ETHER HYDROCHLORIDE (BENADRYL)*

By Thomas H. McGavack

Herbert Elias

and

Linn J. Boyd

(From the New York Medical College, Flower, and Fifth Avenue Hospital, New York City)

Following the demonstration that a series of benzydryl ethers of the general formula

could prevent fatal anaphylactic shock from histamine inhalation in guinea pigs,[31,32] further studies [33,34,35,36,52] have shown its antihistamine action to be more than 600 times that of papaverine. In addition some atropine-like and antiacetylcholine effects have been observed.[6,9,35,52,53] The clinical implications of these facts have been quickly recognized, particularly in relation to the control of allergic manifestations in the skin.[7,8] The occurrence of unpleasant symptoms in these and other[52] early clinical experiences with the drug has raised the important question of toxicity as applied to human beings. Therefore, carefully controlled observations of normal individuals receiving the drug in several times the originally recommended doses have been made. In each subject the various systems of the body have been closely watched and their functions thoroughly appraised. In a previous communication,[41] the scope of the above mentioned survey together with early clinical experiences have been detailed. The purpose of the present report is threefold: (1) to emphasize the positive pharmacological data as gained from the administration of the drug to normal healthy human beings and to patients; (2) to evaluate, at least in part, the therapeutic range of activity of "Benadryl," and (3) to record the unpleasant symptoms or side-effects of "Benadryl" with an analysis of their nature and frequency.

Methods and Materials. More than 60 normal persons and 242 patients have been the subjects of these observations. Of the normal subjects, 21 have been subjected to a complete cycle of examinations pertaining to the major systems and functions of the body. The remainder have been used for the elucidation of one or more of the special pharmacological problems, such as the effects of the drug on the eye or on glucose tolerance. In all normal subjects the standardization of living routine was as previously described.[41] Intravenous glucose tolerance curves were performed according to the method of Thorn[55] slightly adapted to our own needs.[47] Values for "Benadryl" in the blood and spinal fluid were determined by the method originally described by Brodie[4] with some modification.[18] Methods for all other laboratory procedures have been given in detail elsewhere.[41] The majority of all observations were made following the oral administration of the drug. In addition, glucose tolerance curves and blood pressure readings were obtained following a single intravenous dose of 20 to 30 mg., and the effects upon the eye were recorded pursuant to its topical application.

Results. I. Pharmacological Data. 1. *The Antihistamine Effects.* Repeatedly,

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the unpleasant reaction which sometimes attends the administration of histamine in the course of gastric analysis was relieved by the intravenous administration of 20 mg. of "Benadryl." Thus we confirmed in human beings the observations made on small laboratory animals by Kaiser, Lowe and their co-workers.[31-36]

from 150 to 400 mg. daily over periods ranging from 1 to 18 weeks. The results are summarized in Table 1. The variability of this response is illustrated in Fig. 1, and shows the necessity for individualization of dose in each patient. Apparently the severity of this reaction bore no relationship to the patient's clinical con-

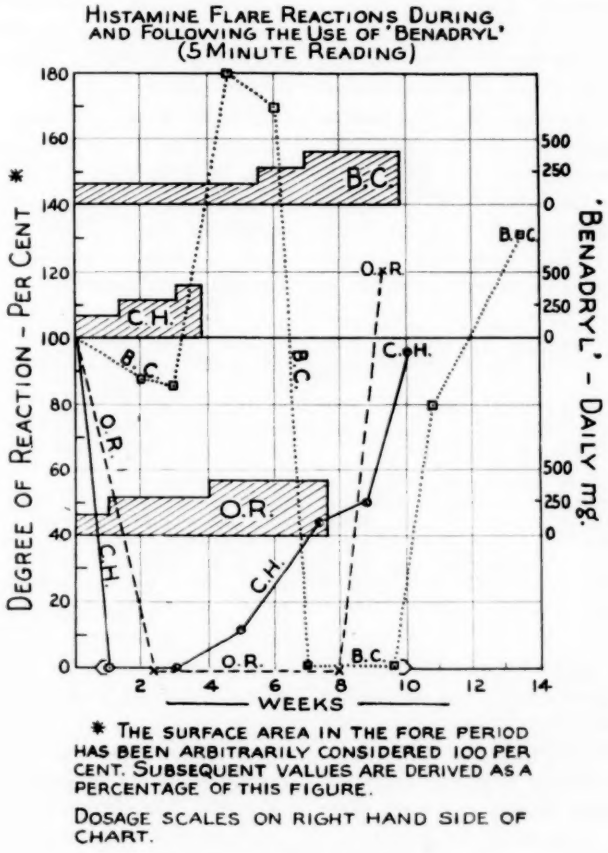
HISTAMINE FLARE REACTIONS DURING AND FOLLOWING THE USE OF 'BENADRYL' (5 MINUTE READING)
DEGREE OF REACTION - PER CENT *
'BENADRYL' - DAILY mg.
WEEKS
B.C.
C.H.
O.R.
* THE SURFACE AREA IN THE FORE PERIOD HAS BEEN ARBITRARILY CONSIDERED 100 PER CENT. SUBSEQUENT VALUES ARE DERIVED AS A PERCENTAGE OF THIS FIGURE.
DOSAGE SCALES ON RIGHT HAND SIDE OF CHART.

FIG. 1.

More specifically, this antihistamine effect was demonstrated in relation to the oral administration of "Benadryl" at various dosage levels in the following ways:

(*a*) Suppression of the dermal response to histamine. The wheal and flare responses of 20 normal subjects and 7 patients were recorded following the oral administration of "Benadryl" in doses of

dition, nor to the presence or absence of some allergic disease. For instance, O. R. (Fig. 1) was an asthmatic of long standing, while B. C. (Fig. 1) and C. H. (Fig. 1) were normal individuals. Despite these wide variations in response from individual to individual it was possible to suppress completely the reaction in any given subject by some dosage well within the therapeutic range. Indeed, the uniform-

ity with which this response could be elicited strongly emphasizes the antihistamine character of "Benadryl" activity and the satisfactory results which have been obtained in a wide variety of skin conditions.[2,7,8,14,15,30,38,39,44,50,51,56,57,61,62]

(*b*) The depression of gastric acidity. Almost as impressive as the influence of "Benadryl" upon the dermal response to histamine was its ability to suppress the secretion of acid by the stomach. As was the case with the "flare and wheal reaction," the daily dose and period of administration necessary to bring about this effect varied widely from subject to subject, but was produced with a single exception in each of 21 subjects upon whom tried. This particular patient responded with a decided increase in gastric acidity, most marked when 400 mg. of drug were given daily; gastric acidity returned to normal within two weeks after the drug was discontinued.

As a rule the change in gastric secretion could be observed within one week after administration of the drug was begun in a daily dose of 150 mg., but in some subjects as much as 400 mg. daily for 2 weeks was necessary to elicit it. It was usually possible to suppress completely the formation of acid by the stomach, in from 1 to 4 weeks when 400 mg. were given daily. For the majority of these subjects the data are fully analyzed elsewhere.[40,41] The averaged results in 5 normal subjects who received 400 mg. of "Benadryl" daily for 3 to 5 weeks are illustrative (Fig. 2). In making these curves, data from the initial or pretreatment gastric analysis have been accepted as 100 per cent in each instance, and subsequent values reckoned as a percentage thereof. The composite curve shown is the averaged value of these percentages.

When "Benadryl" is stopped, from 1 to several weeks are required for the secretion of gastric acid to return to normal. In some instances, the anacidity or hypoacidity gives way to hyperacidity in this release phase.

Inasmuch as histamine has now been accorded an important place in the secretion of gastric acid under physiological conditions,[1,16,46] the suppression of acidity following the administration of "Benadryl" is rather convincing evidence of its antihistamine activity.

TABLE 1.—ERYTHEMA AND WHEAL REACTIONS TO INTRACUTANEOUSLY ADMINISTERED HISTAMINE DURING AND FOLLOWING "BENADRYL" THERAPY

No. Subjects	27	11	18	5	9	4	3
Dosage (mg. Daily)	0	150	300	400	0	0	0
Duration Treatment (weeks)		2.3	3.5	4.0	1.0	2	5
Degree of Reaction:							
Erythema:							
5 min.	100	25	0	0	6	73	138
10 min.	100	11	0	0	15	92	138
Wheal:							
5 min.	100	18	0	0	2	80	120
10 min.	100	14	0	0	17	88	132

(*c*) The decrease in capillary permeability. As determined by fluorescein,[28] the permeability of the capillaries of the lower extremities was decreased by large doses (300 to 400 mg. daily) of "Benadryl" (Fig. 3). Moreover, in a negative way it has been shown that meningeal capillaries, normally more or less resistant to the passage of fluorescein, are not appreciably influenced in this respect by "Benadryl",[17] despite the fact that this drug readily diffuses into the spinal canal to establish levels comparable to those in the blood.[18]

That histamine has a normal role to play in the permeability of tissue capillaries was suggested many years ago. Moon[42] has more recently summarized some of the evidence confirming such an activity. It, therefore, seems logical to

conclude that "Benadryl" probably "tightens" the capillaries through a neutralizing action upon the histamine of the tissue.

2. *The Atropine-like Activity.* The antihistamine activity of "Benadryl" has been fully confirmed by a number of observers.[6,9,10,11,12,13,15,31,32,33,34,35,36,40,41,45,49,52,58,69,60] This is, indeed, the only action of the drug which can be distinguished with certainty. However, attention has been directed also to both an atropine-like effect[6,21,35] and to an anti-acetylcholine influence.[9,52,53] Nevertheless, one must tread cautiously in allocating any particular observation to either one or both of these categories. In the data here presented, a clearcut atropine-like influence seems to have been exerted upon the human eye by the local application of "Benadryl" in an aqueous solution of 0.5% or more. No changes were apparent when the drug was given orally up to 400 mg. daily for several weeks, except for a slight blurring of vision in 10 of 242 patients. In 60 subjects the eyes responded to the topical application of a 0.5% aqueous solution of "Benadryl" by an increase in the size of the pupil in 49, a decrease in visual acuity in 12, and a decrease in ability to accommodate in 43.

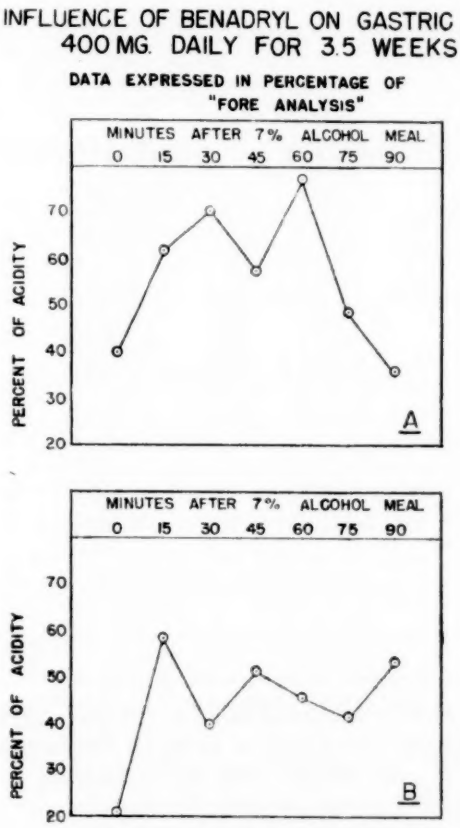

FIG. 2.—*A*, total acid; *B*, free acid.

In 25 subjects, the effects upon pupillary diameter of "Benadryl" alone and of "Benadryl" in combination with epinephrine, homatropine and eserine, respectively, were compared (Fig. 4). The readings on which this chart (Fig. 4) is based were made at the end of 1 hour; the full technic of the tests has been

described in detail elsewhere.[21] Within the limits of experimental error the dilating action of "Benadryl" was not increased by epinephrine, but the speed with which it occurred was hastened so that the response became maximal within 15 minutes instead of 1 hour. "Benadryl" appreciably furthered the mydriatic action of homatropine (from 150%–169%) and antagonized the miotic influence of eserine by increasing the pupillary aperture from 38% of its pretreatment size to 50% of that value.

here to emphasize the point that, unlike sympathomimetic drugs, it may produce a quieting rather than an erethistic effect. Moreover, when large doses of the drug are used (200 or more mg. at a single dose or 600 or more mg. daily), some of the effects upon the sensorium closely resemble those of the belladonna alkaloids.

(*a*) Action on the cardio-vascular system. No disturbances in pulse rate or size of the capillaries was observed in subjects receiving from 150 to 600 mg. daily. As previously mentioned, capillary perme-

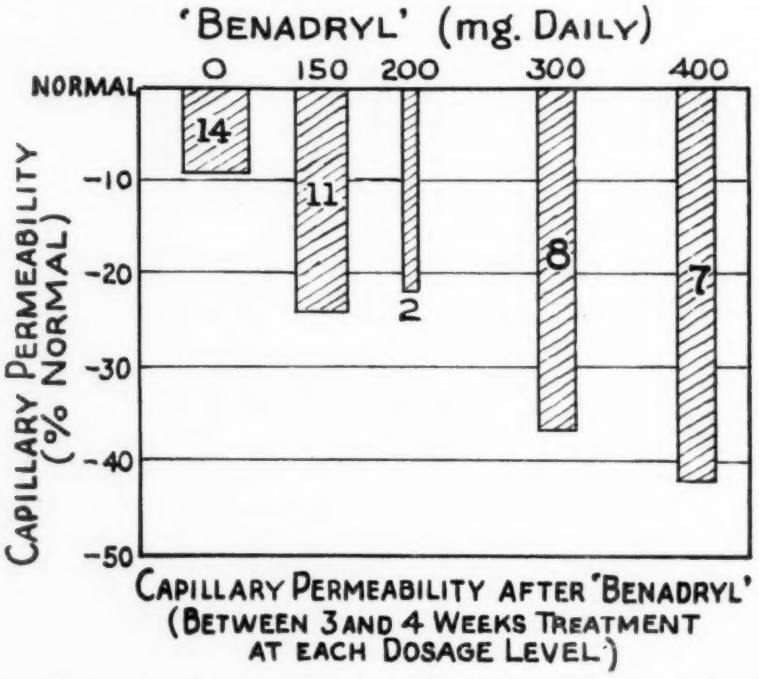

FIG. 3.—Figures on the columns represent the number of subjects at the given level of dosage.

In view of the disturbance in accommodation brought about by "Benadryl," it seems fair to conclude that its action upon the eye following topical application simulates that of the alkaloids of the belladonna group.

3. *Less Well Understood Pharmacologic Effects of "Benadryl."* The influence of "Benadryl" upon the central nervous system will be discussed under toxic reactions. Nevertheless, it seems important

ability was decreased in the majority of instances when 300 or more milligrams of drug were administered daily.

The systolic blood pressure was lowered by 10 mm. or more of mercury in 29 of 74 patients ingesting from 250 to 600 mg. of the drug daily over periods ranging from 21 to 280 days (Table 2). Five of these subjects (6.8%) developed an orthostatic hypotension (Table 2) which was completely asymptomatic in 4. Following a

single dose of 400 mg. of "Benadryl" orally to 14 subjects, a tendency to lowering of the blood pressure, sometimes maintained for several days, was observed. Orthostatic hypotension occurred in 5, as illustrated in patient S. M. (Fig. 5). It seems difficult to consider these actions as atropine-like, unless we concede the point that the more toxic effects of atropine were simulated.[54] Neither do they seem to be an antagonism to acetylcholine, which in itself has a lowering effect upon blood pressure. A vaso-dilatation of blood vessels has been reported in the ears of rabbits following the use of "Benadryl".[45] In view of the fact that the size of the capillaries does not seem to have been altered, it would then appear that the

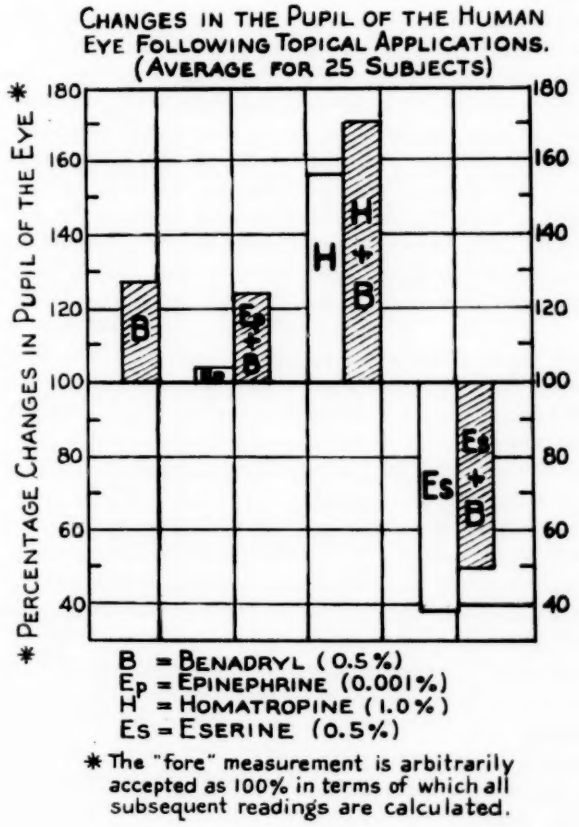

FIG. 4.

TABLE 2.—BLOOD PRESSURE CHANGES IN 74 PATIENTS TREATED WITH "BENADRYL"

	No. Pts.	Dose: Daily (mg.) Range	Dose: Daily (mg.) Aver.	Dose: Total (gm.) Range	Dose: Total (gm.) Aver.	Treatment (Days) Range	Treatment (Days) Aver
No Change*	45	150–600	254	2.2–145.0	15.2	14–311	61
Lowering*	29	250–600	289	5.0–138.0	23.8	21–280	68
Orthostatic Hypotension	5	200–400	360	8.4– 34.8	17.1	21– 90	57

* A variation of 10 points or less from the original figure was ignored. No value was classified as lowered unless repeated pressures at frequent intervals were consistent.

variations in blood pressure may have been due to a prearteriolar or small blood-vessel vasodilation.

(*b*) Action on glucose tolerance. Intravenous glucose tolerance tests were performed upon 14 subjects under standard conditions already detailed.[47] No change in tolerance could be elicited when a single 400 milligram dose of "Benadryl" was given orally ½ hour prior to the beginning of the test. When 20 mg. was given intravenously there was a definite increase in tolerance shown by an average decrease of 69 mg. per 100 cc. in the level for blood sugar ½ hour after the infusion was begun. The total area of these curves for the 4 hour period was 30.1% less than the area of the control curves in the same subjects. Moreover, as compared with curves concomitantly made on 3 additional subjects these variations were statistically significant.[47]

A priori we had more or less expected either no change or a decrease in tolerance in these tests. The reason for the increase observed is not entirely clear. It could be related to a phasic interaction between the drug and the autonomic nervous system, and through the latter to the influence upon pancreas or liver, or both.

Therapeutic Experiences With "Benadryl." Dimethylaminoethyl benzhydryl ether hydrochloride has been used successfully in the treatment of etiologically diversified cases of urticaria, angioneurotic edema, and pruritus,[2,7,8,14,39,41,44,50,56] and in the management of physical allergies.[39,43,61,62] Results have been satisfactory but much less dramatic in the majority of patients with hay fever[24,25,26,37,57] and vasomotor rhinitis.[37] A much smaller percentage of patients with bronchial asthma have obtained relief.[24,25,37,41] In all, we have observed 242 patients with a wide variety of complaints while under treatment with "Benadryl" (Tables 3 A, B, C, D, and E). In view of our knowledge of the antihistamine action of the drug, these cases may be logically divided into several groups:

A. Disease Affecting the Skin, in Which Histamine is Believed to Play a Pathogenetic Role. The drug has been tested in those conditions for which sudden and prolonged releases of histamine are believed to have a pathogenetic relationship.

All of 18 patients with *angioneurotic edema* (Table 3A) were improved by daily doses of "Benadryl" ranging from 150 to 300 mg., and total doses varying from 750 to 15,150 mg. Of the 5 patients designated as "improved" in the table, 3 had complete relief of the edema but not of an associated urticaria. A fourth was relieved of the edema, but was unable to tolerate the drug, even 100 mg. daily in divided dose; on the 5th day after it was stopped the edema recurred. The fifth patient had only 5 days of treatment at the 150 mg. dosage level for a chronically recurring condition. It would appear that well over 90% of the patients with angioneurotic edema can be quickly controlled by a single large dose of the drug, and that recurrence can be prevented by daily doses of from 100 to 150 mg.

All four of the cases of generalized *pruritus* were improved, one completely—a middle aged man in whom the cause of the condition was never discovered. The other patients suffered respectively from senile pruritus, the pruritus of Fox-Fordyce's disease, and pruritus secondary to an emotional upset. The itching in the case of the girl with Fox-Fordyce's disease has been controlled for 5 months with a dose of 250 mg. daily, but there has been little or no recession in the characteristic lesions of the disease.

Of 36 patients with *acute and chronic generalized urticarias*, 26 were completely relieved, 7 showed improvement and 3 were not helped by daily doses of "Benadryl" ranging from 100 to 600 mg. over periods of time varying from 1 to 131 days. Two of these patients were sensitive to the injection of insulin, and doses of 100 mg. daily have been sufficient to keep them completely free of symptoms; the 131 day period of treatment refers to

TABLE 3-A.—RESULTS OF TREATMENT WITH "BENADRYL" IN 242 PATIENTS.
A. DISEASES AFFECTING THE SKIN.

Condition	Total No. Cases	Results C.R.*	I.*	No Relief No.	%
Angio-neurotic Edema	18	13	5	0	0.0
Generalized Pruritus	4	1	3	0	0.0
Urticaria	36	26	7	3	8.3
Allergic Eczema	6	1	2	3	50.0
Neuro-dermatitis	9	1	2	6	66.7
Total	73	42	19	12	16.4

* C. R.—Complete Relief. I.—Improved.

TABLE 3-B.—RESULTS OF TREATMENT WITH "BENADRYL" IN 242 PATIENTS.
B. DISEASES OF KNOWN ALLERGIC ETIOLOGY ((EXCLUDING SKIN).

Condition	Total No. Cases	Results C.R.*	I.*	No Relief No.	%
Bronchial Asthma	36	18	12	6	16.7
(*a*) Intrinsic	12	9	2	1	....
(*b*) Extrinsic	7	2	3	2	....
(*c*) Mixed	17	7	7	3	....
Hay Fever	8	5	1	2	25.0
Vasomotor Rhinitis	11	7	1	3	27.2
Allergic Hydrarthrosis	1	1	0	0	0.0
Total	56	31	14	11	19.6

* C. R.—Complete Relief. I.—Improved.

TABLE 3-C.—RESULTS OF TREATMENT WITH "BENADRYL" IN 242 PATIENTS. C. DISEASES IN WHICH AN ALLERGIC ELEMENT MAY BE PRESENT.

Condition	Total No. Cases	Results C.R.*	I.*	No Relief No.	%
Functional Dysmenorrhea	9	6	2	1	11.1
Spastic colon	15	7	4	4	26.7
Other G. I. Neurosis	10	1	5	4	40.0
Migraine	17	7	5	5	30.0
(*a*) Vaso-constrictor	6	2	2	2	....
(*b*) Vaso-dilator	8	3	2	3	....
(*c*) Not classified	3	3	0	0	....
Ménière's Syndrome	5	1	2	2	40.0
Total	56	22	18	16	28.5

* C. R.—Complete Relief. I.—Improved.

TABLE 3-D.—RESULTS OF TREATMENT WITH "BENADRYL" IN 242 PATIENTS.
D. MISCELLANEOUS CONDITIONS.

Condition	Total No. Cases	Results C.R.*	I.*	No Relief No.	%
Intractable Insomnia	9	3	2	4	44.4
Cardiac Asthma	8	1	3	4	50.0
Hypertension	8	0	2	6	75.0
"Degenerative" C. N. S. Lesions	19	0	4	15	78.9
Epilepsy	3	0	0	3	100.0
Heterogeneous Group	10	0	0	10	100.0
Total	57	4	11	42	78.9

* C. R.—Complete Relief. I.—Improved.

TABLE 3-E.—SUMMARY OF RESULTS OF TREATMENT WITH "BENADRYL" IN 242 PATIENTS.

Group	Total No. Cases	Results C.R.*	I.*	No Relief No.	%
A. Diseases of the Skin with an Allergic Component	73	42	19	12	16.4
B. Other Diseases of Known Allergic Etiology	56	31	14	11	19.6
C. Diseases in which an Allergic Element *May* be Present	56	22	18	16	28.5
D. Miscellaneous Conditions	57	4	11	42	78.9
Totals	242	99	62	81	....
Per Cent	100.0	40.9	25.6	33.5	....

* C. R.—Complete Relief. I.—Improved.

one of these insulin-sensitive individuals. In several of the acute conditions a single dose of 100 mg. served to give complete relief. Of the 3 patients listed as obtaining "no relief," one contracted a chronic urticarial condition overseas in the African theatre of war, associated at times with a weeping eczematous eruption. A second patient with chronic urticaria of unknown etiology stopped the drug after taking 200 mg. daily for 3 days because of untoward reactions, although the lesions were improved. The third received the drug for a single day with improvement in itching but no objective change in the appearance of the lesions.

The causes of these urticarias included drugs, foods, and contactants; in some instances, psychic factors and sensitivity to bacteria within the respiratory passages were believed to excite the attacks. As soon as the condition was controlled by treatment, offending foods and drugs could be ingested without recurrence of the condition as long as the drug was continued and usually for several days thereafter. One patient with insulin sensitivity was treated continuously for 2 weeks since which time (3 months) she has needed no further medication to keep her symptom free despite the maintenance of her insulin regime.

Three of 6 patients with *allergic eczema* were not improved by "Benadryl." However, no daily dose of more than 200 mg. was tried in this group, and in two instances the alkamine ether was only continued for 3 days. In no instance had the condition been present less than 9 months, and in the one patient who completely recovered, it had lasted for 6 years (since birth) and disappeared after 4 days' treatment with 200 mg. daily; following 48 more days of treatment with 150 mg. daily, the patient has remained completely free of symptoms for 4 months.

Neurodermatitis was much more difficult to control than either of the conditions just mentioned. Two-thirds of the group were relieved but the time necessary for a satisfactory response varied from 17 to 60 days (except for 1 patient improved in 3 days) on daily dosages ranging from 150 to 400 mg. Historically and objectively there was nothing prior to treatment which distinguished the improved from the unimproved group.

B. DISEASE OF KNOWN ALLERGIC ETIOLOGY (EXCLUDING SKIN). Fifteen of the 36 patients with *asthma* were in status asthmaticus when treatment was begun. There were no consistent criteria by which those cases that did respond could be distinguished *a priori* from those that failed to do so. Our percentage of patients with bronchial asthma that obtained relief from "Benadryl" in the present series is considerably higher than that reported by other workers.[15,25,26,30,37,57,63] If our interpretation of the literature is correct, we believe the apparent discrepancy lies in the mode of application of the drug, and the results which may be expected from its administration.

Attention to several simple rules may materially improve the results to be obtained by the use of the drug. Acute attacks may be prevented in many instances if from 2 to 4 capsules are taken with the advent of the very first symp-

toms. No dramatic response can be expected from any dosage level (up to 100 mg. every 4 hours tried) in the patient with status asthmaticus, or even in the individual whose attack, though not too prolonged, is well established before the drug is administered. In status asthmaticus, the first sign of improvement is usually seen by the end of the first 24 hours, and other substances, such as aminophyllin which had previously been ineffective, begin to evoke a response. Once the patient is free of the immediate attack, he should be placed upon a daily dosage level sufficient to ward off recurrence. As a rule 200 mg. daily, of which 100 mg. is given at bed time, will be sufficient to maintain the patient free of symptoms, although as much as 400 mg. daily with 150 mg. taken at bed time has been necessary. In addition an extra dose of 50 to 100 mg. is advised at the first warning of distress. One patient who has had daily nocturnal attacks for 3 years and diurnal distress three times weekly for 3 years, has been maintained completely free of discomfort during the past 4 months with a total daily dose of 400 mg. Moreover, he has not experienced any "side-effects" from so large a dose of "Benadryl". It is further clear, that patients who already have secondary changes in the lung and heart will not respond as satisfactorily as those who are free thereof. Whether or not the asthma is intrinsic, extrinsic or mixed seems to make very little difference in the response. In asthma and in other allergies where a long continued regime of treatment must be followed it may be necessary to increase the initially effective dose to maintain the same degree of response. Apparently a tolerance according to the principle of Le Chatellier-Braun is involved in this phenomenon.

About 75% of the patients with *hay fever* and *vasomotor rhinitis* have been relieved of their attacks with "Benadryl" (Table 3B). As a rule, these cases are quite readily controlled on small doses of the drug—from 100 to 150 mg. daily. Two of the 5 recorded failures in these 2 groups were only treated for 2 days with a total dose of 300 mg. each. A third had an associated "widespread eczema" and "neuro-dermatitis." In the other two cases, the drug was discontinued because of "side reactions."

C. Diseases in Which an Allergic Element May be Present. Six of the 9 patients with a "*functional*" *dysmenorrhea* had been treated hormonally without success. Two of this group of patients had an associated spastic colon and 2 others a gastrointestinal neurosis with epigastric manifestations. All of these were relieved by "Benadryl". The 1 patient who obtained no relief from her dysmenorrhea with "Benadryl" had a thyrotoxic goitre with malignant exophthalmos. Four of 7 of these patients have been carried through 4 or more periods, and 3 additional patients through 2 cycles, while 2 have been watched during one. The necessary dosage, usually 200 mg. daily, was begun 3 or 4 days before the period was due. If there was any sign of pain, additional doses were added at 3-hour intervals.

While the role of histamine in the production of functional dysmenorrhea may be open to doubt, the association of such a condition with disturbances in the balance of the autonomic nervous system appears to have been accepted.[5,19,20,22] The results certainly justify an extended trial.

Continued treatment was necessary to relieve patients with a *spastic colon*. The necessary daily dose rarely exceeded 200 mg.; 1 patient has remained comfortable after 8 months of treatment with 100 mg. daily, and has gained 15 pounds in that time. There was no apparent difference in the presenting manifestations of those patients who did and those who did not respond. The question of the role of histamine in the pathogenesis of spastic colon is perhaps a mooted one, but at least some of the evidence favors a positive relationship.[3,46]

Other gastro-intestinal neuroses, which were for the most part psychic in origin, were not materially improved by "benadryl".

Some cases of *migraine* obtained dramatic relief from "Benadryl", either in a single dose of 100 mg. by mouth or from an intravenous injection of 20 mg. Whether the headache fell into the so called vasoconstrictor or vasodilator group seemed to make little difference in the result.

The 1 patient with *Ménière's syndrome* who obtained complete relief with "Benadryl" was symptom free 20 minutes after a single oral dose of 50 mg. and remained without attacks for 2 months by the daily use of a similar dose. This was the only 1 of the 5 patients in which a true, or so-called idiopathic type of Ménière's syndrome was believed to exist. Two of the others were on a hypertensive basis and the remainder were thought to be secondary to arteriosclerosis.

D. Miscellaneous Conditions. Because of the drowsiness so frequently experienced following the administration of "Benadryl", 9 patients with insomnia who were chronically habituated to the derivatives of barbituric acid were given "Benadryl" at bed time in doses ranging from 100 to 300 mg. Two of the 4 patients whose sleep was not improved had arteriosclerotic heart disease with some degree of chronic left ventricular failure. A third slept satisfactorily following the use of 3 capsules (150 mg.) nightly, but was "woozy" and fatigued all of the next day. In those patients whose sleep was satisfactory, there was a tendency for a decreasing effect as the drug was continued, so that one patient ceased to obtain relief by the end of the second week despite increasing doses, and all but one have had to increase the dose materially. If the drug was used discontinuously, the effects were much better maintained. The relationship of these findings to the drowsiness experienced by other patients who need the drug for the treatment of allergy is obvious.

Attempt was made to improve the status of patients with a *cardiac asthma*. The spastic wheezing asthmatic respiration of these individuals was routinely improved with large doses (between 400 and 600 mg. daily in divided dose). Inasmuch as 50% of the individuals showed improvement its further trial in this condition appears to be warranted, and the presence of a histamine release factor in severe forms of left ventricle failure is suggested.

Because "Benadryl" has produced a reduction in blood pressure in many subjects (Table 2) a therapeutic trial was made in 6 cases of essential *hypertension* and in 2 with arteriosclerosis and hypertension. Neither of the latter were helped. The blood pressures of each of the remainder were lowered but the clinical condition improved strikingly only in 2; in 1 of these the changes initially observed justified the classification of a malignant phase of essential hypertension. In this patient, after 8 months of treatment with daily doses of 300 mg., blood pressure is normal, no new lesions have developed in the eyes, and previous symptoms have disappeared. No attempt should be made to evaluate these findings until a large series of patients has been observed over a relatively long period of time.

Of the patients with "*degenerative*" *lesions of the central nervous system*, 4 had multiple sclerosis, 4 paralysis agitans, 3 progressive muscular dystrophy, 3 spinal muscular atrophy, 5 a long since inactive tabes dorsalis. In view of the drowsiness, dizziness, and at times incoordination produced by "Benadryl", and the congestion of the choroid plexus observed in animals intoxicated with it, it seemed justifiable to test its usefulness in some of the conditions of the nervous system associated with lesions in and around the thalamus and basal ganglia. Three of the 4 patients with paralysis agitans, all of an arteriosclerotic type, believed they experienced subjective improvement as a result of the long continued use of the drug. A change in tremor and work performance, observed in two of these who received the drug for

relatively long periods of time (for 5 and 15 months, respectively), was not entirely accounted for on a psychic basis. One patient with multiple sclerosis has also been listed as improved although a purely psychic response in his case is not ruled out. There was no change in the status of any of the other 19 patients in this group.

In view of the sedative effect of "Benadryl" in some instances, it was tried in 3 patients with *idiopathic epilepsy* of the grand mal type. In each instance a very definite aggravation of status was observed. It is difficult to interpret such a finding, but it may perhaps be related to blood vessel tonus and to altered capillary permeability.

ity. Despite the ability of "Benadryl" to dilate blood-vessels[45] the intermittent claudication of an arteriosclerotic individual was not relieved. It is possible that pruritus ani may respond to the local application of "Benadryl" but one instance of this condition was not relieved by its oral ingestion in doses of 600 mg. daily for 3 days.

The Nature and Frequency of Toxic Reactions to "Benadryl". In order of their frequency, drowsiness, dryness of the mouth, dizziness, weakness and fatigability, incoordination and lightheadedness, and blurring of vision were encountered commonly as untoward reactions associated with the oral administration of "Benadryl" (Table 4). In conjunction

TABLE 4.—UNTOWARD REACTIONS IN 242 PATIENTS RECEIVING "BENADRYL"*

Condition	Number and Per cent of Reactions Observed on Daily Dose of (mg.)‡						Total Reactions
	50	100	150	200	300	400 or more	
Number of Patients on Each Dose†	28	20	135	79	74	44	...
Sleepiness	5 (18)	3 (15)	55 (40)	21 (26)	11 (15)	10 (22)	105
Dryness of the Mouth	1 (3)	0	28 (20)	5 (6)	8 (10)	6 (13)	67
Dizziness	0	0	28 (20)	12 (15)	5 (6)	9 (20)	54
Weakness and Easy Fatigability	1 (3)	1 (5)	19 (14)	4 (5)	5 (6)	6 (13)	36
Incoordination and Lightheadedness	1 (3)	1 (5)	6 (4)	1 (1)	0	2 (5)	11
Blurring of Vision	0	1 (5)	5 (3)	3 (4)	0	1 (2)	10
Totals	8	6	141	79	47	44	283

* 131 of the 242 showed some one or more unpleasant symptoms following the administration of "Benadryl".

† When "reactions" occurred in any given individual at more than one dosage level, they are recorded separately for each; hence, the apparent discrepancy between the total number of patients in whom untoward symptoms were observed and the total number of such symptoms.

‡ Figures in parenthesis represent the approximate percentage of subjects affected at the given level of dosage

In the "*heterogenous group*" of patients were included one with duodenal ulcer, one with cirrhosis of the liver, one with Sudek's atrophy, 3 with thyrotoxicosis, 2 with cardiospasm, one with generalized arteriosclerosis, and intermittent claudication, and one with pruritus ani. None of these were improved. It had been hoped that the tremor of hyperthyroidism might be relieved. No atropine-like action could be observed in the cases of cardiospasm. The patient with duodenal ulcer gave no evidence of clinical improvement despite a marked decrease in gastric acid-

with the incoordination and lightheadedness, thickness of speech and impairment of memory were often seen. The blurring of vision was not entirely due to the disturbances of accommodation to which reference has already been made.

Manifestations which occurred and which may have been directly due to the action of the drug included headache, nausea, anorexia, "butterflies in the stomach", "all-goneness at the pit of the stomach", "restlessness of the legs", "buckling at the knees", excessive perspiration,

faintness, intolerance to noise, and ringing in the ears.

In all, 131 of 242 patients developed some unpleasant symptom. The highest percentage of reactions was observed in patients who received 150 mg. of "Benadryl" daily. In many of these the symptoms disappeared while the drug was continued at the same dosage level. The mildness of these distressing symptoms is further emphasized by the fact that they necessitated stopping "Benadryl" in but 5 instances. In 3 of these, a feeling of extreme fatigue associated with an "all-gone sensation" at the pit of the stomach was more distressing than the allergic condition for which relief was obtained. In a fourth subject, sleepiness due to the drug was more incapacitating than her asthma. In the fifth patient, a case of spastic colon, dizziness, nervousness, fatigue, dryness of the mouth and some incoordination all occurred at levels of dosage (250 mg. daily) necessary to control her symptoms, and were so severe that she refused further medication at any dosage level.

Each of the symptoms recorded in Table 4 has been seen at every dosage level used. Drowsiness was by far the most easily evoked, and often a single dose of 50 mg. necessitated the use of caffeine or other similar stimulant to keep the subject awake during the 2 to 3 hours immediately following its administration. None of the other symptoms has been incapacitating until daily doses of 300 or more milligrams were used, or when a single oral dose of 400 mg. was administered.

Tolerance for the drug improves rapidly as its administration is continued. In 69.4% of the patients noting untoward symptoms while taking 150 mg. daily, these were improved by the end of the third day and had disappeared completely within 10 days despite the continued use of the drug. In 28.1% the dose was reduced with disappearance of unpleasant symptoms and was later increased to its former level and beyond without recurrence. In 2.5% the drug could not be used at any dosage level without distressing manifestations. If the drug was stopped for 10 days or longer, the resumption of its use might again be associated, although not necessarily, with the originally experienced side effects, to which tolerance could again be acquired.

A decrease in the unpleasant effects produced by "Benadryl" was occasionally associated with a decrease in the effectiveness of its action against the condition for which it was being administered therapeutically. An increase in dosage usually overcame this problem and was rarely associated with a recurrence of the "toxic" manifestations for which tolerance had been acquired.

The exact nature of many of these toxic symptoms is not clear. The combination of drowsiness, dizziness, lightheadedness, thickness of speech, slight incoordination of movements, and impairment of vision are quite suggestive of a hyoscine-like action. Even the lowering of blood pressure seen with the larger doses utilized for prolonged periods of time may be similarly interpreted.

The Question of Dosage. How much "Benadryl" shall we give and how long shall we use it? The practical considerations of the two points raised in this question hinge upon the fact that "Benadryl" blocks the action of histamine in a quantitative manner and is utilized in the process. Therefore, the matter of dosage becomes a highly individualistic one, varying from patient to patient and often in the same patient from time to time. For any one of the conditions in which the drug has been found useful, we have employed successfully as little as a single capsule (50 mg.) daily in some instances, and in others have needed as much as 600 mg. daily. Above the latter dosage we have not tried the drug. There is certainly no rule of thumb which covers all cases. However, experiences to date afford us a few general principles.

1. All ambulatory patients should begin treatment with 50 mg. three times daily. If well tolerated the dose may be rapidly

increased—even doubled or trebled—within 24 to 48 hours.

2. The first dose of drug should be given at a time when the patient will not be called upon to perform skilled movements depending upon acts of judgment, for should he prove to be sensitive to the drug, irresistible drowsiness, or perhaps dizziness or blurring of vision may materially interfere with his activity, or even endanger his life. If this dose causes no distress, the patient need have little fear of subsequent disturbances, except in the rarest instance.

3. If the drug has been discontinued a considerable length of time, dosage should be resumed as though the patient had never previously received it.

4. Some diseases appear to respond more readily and at lower dosage levels than do others, although it cannot be overemphasized that each patient must be thoroughly individualized in this regard. In a general way, however, we have been successful with smaller doses (around 150 mg. daily) in such conditions as hay fever, hyperesthetic rhinitis, and Ménière's syndrome. The greatest extremes of dosage have been necessary in such conditions as angioneurotic edema, generalized pruritus, urticaria, allergic eczema, spastic colon, and migraine—varying from 50 to 600 mg. daily. Larger to largest doses have always been necessary to control bronchial asthma, neurodermatitis, functional dysmenorrhea, intractable insomnia and cardiac asthma, none of these responding readily below a dosage level of 200 mg. daily, and the majority demanding the continued use of 300 to 400 mg. daily. Indeed, it is now our rule to start patients with bronchial or cardiac asthma on 600 mg. daily, usually reducing to 400 mg. daily after 24 hours. However, we have maintained the initial dose for 1 week without ill effects. Four hundred mg. has been administered daily for as much as 160 days, during which time the patient has been completely free of attacks formerly occurring every night and usually at some time during every day; a lesser dose was ineffective. In connection with asthma, it should be stressed that the nature of "Benadryl" activity does not adapt it well to the *immediate* control of an already fully developed acute attack. It will prevent an attack, and it will gradually bring status asthmaticus fully under control. In other words, it cuts off the supply of available reactive histamine, but is relatively ineffective against the tissue responses already initiated by that substance.

Intractable insomnia usually responds best to a single large dose of the drug at bed time. Usually 100 mg. is sufficient; occasionally, 150 mg. will be required. Sometimes the latter dose is followed by a "hangover" the next day.

5. The duration of treatment with "Benadryl" appears to be limited only by the requirements of the treated individual. We have given 400 mg. daily for more than 200 days without any subjective or objective evidences of untoward reaction. Patients with chronic dermatologic conditions, hyperesthetic rhinitis, chronic bronchial and cardiac asthma may all demand prolonged courses of treatment.

6. The beneficial influence of "Benadryl" may last for considerable periods of time after the drug has been discontinued, even though the total period of treatment was short. One patient with hyperesthetic rhinitis of 15 years' duration with nearly continuous symptoms has been free of any attacks for 6 months following one week of treatment with 100 mg. daily. A child of 9 years with allergic eczema dating from the first year of life received 2 weeks' treatment with 150 mg. daily. There was no recurrence for 3 months. Following a second similar course of treatment, there has been no recurrence for 6 months.

We have dwelt somewhat at length upon the question of dosage, for it is apparent that many failures to obtain best results from the drug have been predicated upon the hesitancy of the physician to vary the amount given. No "rule of thumb" dosage chart seems advisable in the present state of our

knowledge. The nature of the disease and the individual reaction both play a part in determining the optimum dose in each individual instance.

Summary. 1. Sixty normal subjects and some of 242 patients have been subjected to extensive clinical study while receiving dimethylaminoethyl benzhydryl ether hydrochloride ("Benadryl"). Among the positive effects observed were:

(*a*) Suppression of the dermal response to histamine in all of 27 individuals studied.

(*b*) A depression of gastric acidity in 20 of 21 subjects for whom such analysis was made.

(*c*) An atropine-like action upon the eye in 43 of 60 subjects following the topical application of the drug in a 0.5% solution.

(*d*) A lowering of blood pressure of more than 10 mm. of mercury in 29 of 74 patients when large doses of the drug were used; and orthostatic hypotension in five of these subjects.

(*e*) An increase in glucose tolerance following the intravenous administration of a single dose of 20 mg. "Benadryl"; and no change in tolerance following a unit dose of 400 mg. orally.

2. Two hundred forty-two patients have received "Benadryl" over periods of time varying from 1 day to 15 months. More than 90% of all patients with angioneurotic edema, generalized pruritus, urticaria, and allergic hydrarthosis were relieved. Over 80% of all patients with bronchial asthma and functional dysmenorrhea were improved. Between 50 and 80% of all patients with allergic eczema, vasomotor rhinitis, hay fever, spastic colon, other gastro-intestinal neuroses, migraine, Ménière's syndrome, intractable insomnia and cardiac asthma were materially helped. Other conditions in which the drug was tried included neurodermatitis, hypertension, degenerative lesions of the central nervous system, epilepsy, duodenal ulcer, cirrhosis of the liver, Sudek's atrophy, cardiospasm, intermittent claudication, thyrotoxicosis and pruritus ani.

3. Effective dosages of "Benadryl" ranged from 50 to 600 mg. daily. Initial clinical responses usually followed within 20 minutes after the first dose, but were often delayed, as for instance in bronchial asthma, for from 12 to 30 hours. Maintenance doses have varied from 50 to 400 mg. daily.

4. Untoward side effects of "Benadryl" have been observed with unit doses of 50 mg., but may not occur with single doses as large as 400 mg. nor with daily doses of 600 mg. continued for periods up to 16 weeks. These "toxic" manifestations included, in the order of their frequency of occurrence, drowsiness, dryness of the mouth, dizziness, weakness and easy fatigability, incoordination and lightheadedness and blurring of vision. Uncommonly seen were headache, nausea, anorexia, all-goneness at the pit of the stomach, buckling at the knees, restlessness of the legs, excessive perspiration, faintness, intolerance of noise, and ringing in the ears. A tolerance is usually built up quickly against these unpleasant symptoms. In the majority of instances this occurs so rapidly that the dosage of drug used at the time of their occurrence does not need to be altered.

Conclusions. "Benadryl" is an alkamine ether with a powerful antihistamine action. This is clearly indicated by its ability to suppress completely the dermal and gastric responses to histamine, and to decrease capillary permeability. These effects are further demonstrated through the clinical relief afforded patients suffering with diseases in which sudden and/or prolonged releases of excessive quantities of histamine play a pathogenetic role.

An atropine-like activity for "Benadryl" is suggested by its effects upon the eye when applied topically. The variations in blood-pressure may simulate one phase of the action of atropine.

Disturbances in the sensorium observed in some of the patients receiving the drug have suggested a hyoscine-like action. Moreover, the cardiovascular manifesta-

tions of the drug are compatible with the known influence of hyoscine in one phase of its action.

From the clinicians' point of view, "Benadryl" is an exceedingly potent antihistamine and antispasmodic drug which lacks unpleasant cardiovascular and nervous side effects attendant upon the use of sympathomimetic agents such as epinephrine, ephedrine and benzedrin. Toxic reactions, while common, rarely preclude its continued use.

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THE INTRAVENOUS USE OF HUMAN ASCITIC FLUID IN SHOCK, NEPHROSIS AND ALLIED CONDITIONS

By Richard D. Molina, M.D.,

Hermogenes A. Santos, M.D.,

and

Mariano M. Alimurung, M.D.,

Department of Medicine, Faculty of Medicine and Surgery, University of Santo Tomas; Manila, P. I.

In 1938, Davis and White[1] utilized human ascitic fluid successfully as "a substitute for blood in experimental secondary shock induced by graded bleeding," at the same time observing the "absence of any deleterious effect in their experimental animals." A few months later, Choisser and Ramsey[2] reported similar success in primary shock. Working along this line, one of us (H.S.) et al.[3] conducted experiments to verify such reports, and in 1940 reported equally encouraging results in the management of histamine shock in dogs, all of which survived, "the blood pressure rising above the shock level and back to the initial level even one hour after the cessation of the treatment, without any apparent deleterious effect." In human clinics, however, the use of human ascitic fluid has been very limited, as Barr[4] remarked that same year. Under the circumstances we shall here describe, during the Japanese occupation of the Philippines, these few studies made on this subject, however, turned inspiring enough for us to dare try it in actual human cases and enjoy the privilege of observing its good results. The cases herein reported are, to date, the first of their kind in the Philippines. It is, therefore, mainly to incite more interest towards the proper appraisal of this therapeutic measure that we report these few cases in view of the very encouraging results we observed.

Case 1. *Our Trial Case.* Our trial case was a male Filipino, of middle adult age, admitted into the medical service as a case of portal cirrhosis. Ascitis and edema of the legs were marked. Repeated injections of salyrgan gave temporary relief, as the diuresis that followed each injection eliminated a great portion of the edema. However, both the ascites and edema of the legs reappeared days after the mercurial injections. The ascitic fluid was a transudate.

We then tried injecting into the patient his own ascitic fluid. Being our first case, the amount injected was only 5 cc., with our attention focused more on the possible untoward effects rather than the probable therapeutic results. The patient was watched continuously for the next 24 hours, particularly for cardiovascular developments.

Fortunately, no untoward result whatsoever was noticed, not even a mild febrile reaction. The injection was, thus, later repeated, until the single dose reached 20 cc. In all, no serious ill effects were observed. We repeat, however, that our main purpose in this trial case was to see any possible untoward effects. We did not then entertain its therapeutic potentialities in portal cirrhosis. Rather, these trials were inspired by our search for a possible substitute for other parenteral fluids, as whole blood, plasma, Ringer's solution and others, which, however ideal, were evidently disappearing from our armamentarium during those occupation days.

It must be mentioned how cases of hypoproteinemia were on the up-trend during those days, as a natural result of food scarcity. From these cases easily developed varying states of shock, especially when severe diarrhea and vomiting precipitated its rapid onset after the intake of some "spoiled food," indicating how frantic the struggle for existence then. From our trial case, therefore, we not only obtained our first clinical observations but also served as our first source of ascitic fluid.

CASE 2. *Portal Cirrhosis Developing Collapse after Sudden Perforation of Peptic Ulcer.* C. F., a 60 year old male Filipino, was admitted into the medical service on February 15, 1944, because of generalized abdominal enlargement and epigastric pain.

Evidences of the portal cirrhosis were the ascites and edema of the legs; the bromsulphalein test which gave a retention of 18% in the half hour specimen and about 10% at the hour. The ascitic fluid was a transudate, with nine grams per liter of protein. The blood NPN was 25 mgm. per 100 cc. The urine voided was around 800 cc. in 24 hours.

The existence of peptic ulcer was also supported by the history of recurrent attacks of epigastric pain for 3 years then, especially so when hungry and relieved by food, alkali and hot water bag application.

On February 28, he developed melena. The next day, acute abdomen became evident, with the blood pressure dropping to 90/68 mm. Hg. and the pulse rate going up to 130 per minute. Fluoroscopy revealed pneumoperitoneum. The case was immediately operated upon, revealing a perforated peptic ulcer. Hypodermoclysis of 400 cc. of Nor. Salt Sol. was given, simultaneous with venoclysis of ascitic fluid amounting to more than 100 cc. given during the operation. No untoward results were observed. The patient continued in the surgical service a whole week after the operation, with the peripheral circulatory failure never completely controlled. No second venoclysis was given as no more fluid was then available. In fact, no other fluid could be obtained for intravenous administration. With hypodermoclysis and circulatory stimulants, the patient's struggle finally gave way. It can, however, be definitely stated that the ascitic fluid given during the operation proved to be innocuous.

CASE 3. *Nephrotic Syndrome.* In this third case, we tested the use of ascitic fluid as a possible diuretic and remedy in hypoproteinemia of nephrotic nature, considering the relatively higher protein content of the ascitic fluid and its possible use as a substitute for other recommended fluids, as acacia solution and lyophile serum, both of which were evidently out of reach during those days.

J. T., a 12 year old male Filipino, came to the service on April 22, 1944, with abdominal enlargement and swelling of the lower extremities. The present attack of edema was the second in a period of 4 months.

The diagnosis of nephrotic syndrome was supported by the marked anasarca, the normal blood pressure of 104/90 mm. Hg., the hypoproteinemia of 5.1 gm. %, and the inverted albumin globulin ratio of 1:1.40. Furthermore, there was pleural effusion in the right thorax. The urine exhibited marked albuminuria, with 1+ granular casts, 1+ pus cells and 2+ red cells.

On further study of the etiology of the syndrome, the abnormal equilibrium between the intravascular and extravascular fluids became our main concern. For immediate relief, paracentesis abdominis was performed, collecting a liter and a half of clear ascitic fluid.

Then on May 4, sterile human ascitic fluid, obtained from a cirrhotic patient, was given intravenously. The patient complained of some tightness of the chest, as we reached the 100 cc. level. So, further administration was suspended. We noticed that the injection was going on quite rapidly, and it was to this that we later ascribed the slight untoward effects. At noon time, he developed some chills and headache, and the temperature rose up to 38.9° C. One half cc. of 1:10,000 adrenalin solution was immediately given hypodermically. In the same afternoon, everything subsided. The remarkable results, however, more than made us surprised as the following days the patient began to eliminate large amounts of urine. From a 24-hour output of from 200 to 300 cc. before the injection, he urinated up to 2.5 liters daily, with a consequent drop of body weight from 37 kilos to 25 in less than 5 days. The diuresis continued at more than a liter of urine in 24 hours even after that immediate response, which thus prevented the reproduction of the former anasarcic state.

On May 16, a second intravenous injection was given, this time with only 20 cc., done so purposely to test whether with smaller amounts diuresis could also be obtained. The record, however, shows no further increase in urinary output, although the output maintained itself at the same pace of more than a liter. No untoward effect was observed in this second injection, as it was then given very slowly. To evaluate the results better, all other diuretics, such as

potassium acetate, were suspended days before the first intravenous injection of ascitic fluid. Even the fluid intake was controlled, to avoid any possible effect from an increase of extraneous fluids.

On June 3, the patient was allowed to go home, with practically no edema, except for some puffiness of the eyelids early in the morning, with the body weight at 25 kilos, and still with a daily output of more than a liter of urine.

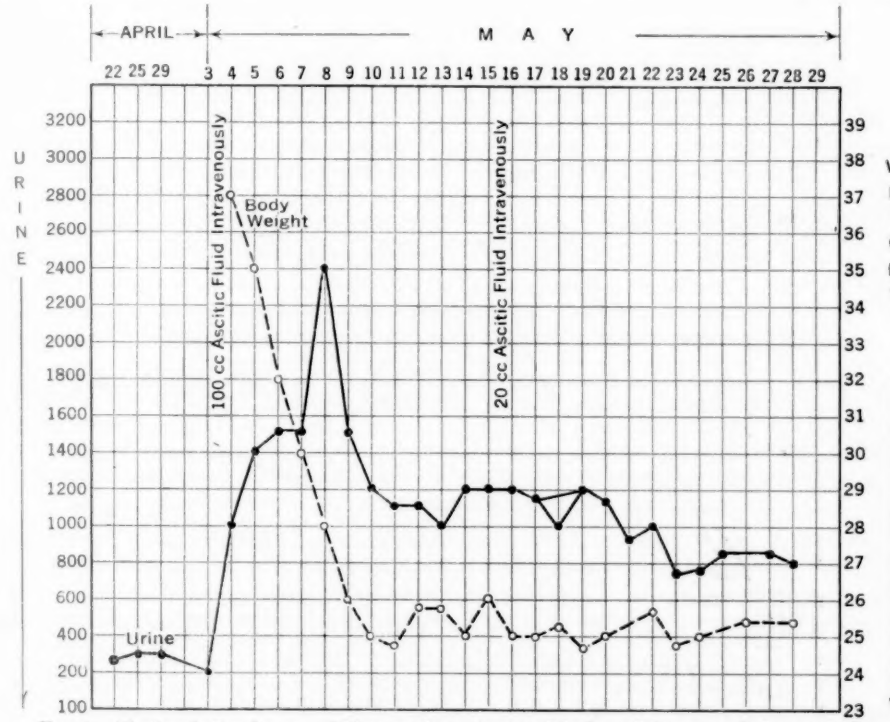

FIG. 1.—Nephrotic Syndrome. 24 hour urine output and body weight curves before and after intravenous injection of ascitic fluid.

CASE 4. *Case of Shock After Severe Diarrhea and Vomiting, Probably Due to Food Poisoning.* It was in this fourth case that we really met the condition for which we originally intended the ascitic fluid. The case was one of severe shock, rapidly developing after intense diarrhea and repeated vomiting due probably to food intoxication.

F. R., male, Filipino, 40 years old, was brought as an emergency case at 8:50 A.M. of Sept. 13, 1944, in a state of collapse. The trouble started the previous night as abdominal pain, followed by diarrhea and vomiting. This illness was closely associated to the taking of some "cassava" a few hours previous to the onset of the whole syndrome. No fever nor tenesmus was noticed by the patient. The stools were at first hard, but soon became soft, loose and finally completely watery. Collapse set in within three hours of almost continuous bowel movements.

The temperature was 35.4° C., the pulse imperceptible, the heart sounds practically inaudible, the blood pressure unrecordable, the eyeballs sunken, and the skin with cold clammy sweats. Marked paleness was evident. Consciousness, however, was still present, the patient complaining of muscle cramps, especially of the calf muscles. *Laboratory reports:* 5,150,000 red blood cells and 11,500 leucocytes with practically normal differential count. The stools presented no macrophages nor parasites, with few leucocytes and completely watery in consistency.

He was treated with blankets and hot

water bags to the extremities; circulatory stimulants; and hypodermoclysis of 500 cc. of N.S.S. were given as initial measures. Then 500 cc. of sterile human ascitic fluid was administered by slow intravenous injection. No untoward effect was noticed during and after the injection. At 1:25 P.M. of that same day, the pulse became perceptible ascitic fluid was then given at 5:00 of that same afternoon.

The next morning, the patient was evidently already out of danger. At 8:00, his temperature was 36.1° C., the pulse already full, with a rate of 100 per minute, restlessness subsided and the facies revealed the onset of convalescence. At 10:00 A.M., the

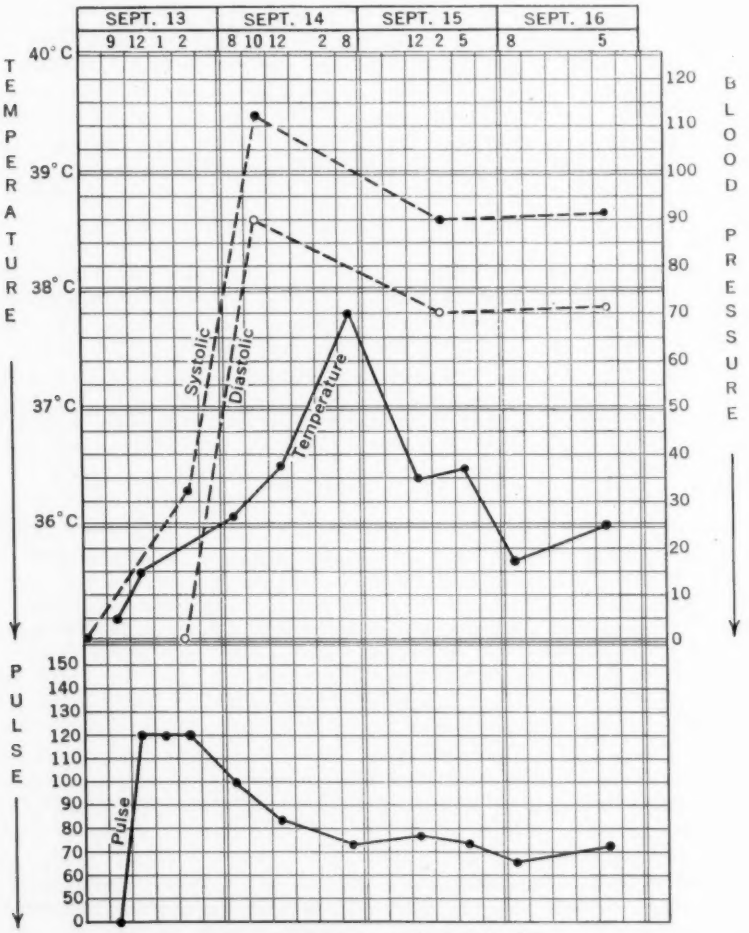

FIG. 2.—Shock, due to food poisoning.

for the first time since the onset of the collapse, with a rate of 120 per minute, though still weak and easily collapsible. Temperature was 35.6° C. The blood pressure was still undetectable. At 2:00 P.M., the sphygmomanometer finally registered a systolic reading of 32 mm. Hg. Another intravenous dose of 500 cc. of blood pressure reached already 112 systolic and 90 diastolic; and at noon, his temperature reached 37.8° C. with the pulse rate of 75 per minute. All medications were then stopped, and only food and rest were prescribed. Two days later, he left the hospital completely cured.

OTHER CASES. *Two Cases of Shock After Perforation of Peptic Ulcer.* After the above mentioned cases, 2 other cases received intravenous injections of human ascitic fluid. They were cases of shock, following perforation of peptic ulcers.

The ascitic fluid was given as emergency measure, administered intravenously during the surgical operation. The amounts given varied, according to the available supply of ascitic fluid. However, no less than 50 cc. was given in each case. These 2 cases unfortunately succumbed a few days after operation, due to various conditions. We can safely state, however, that no untoward effect was noticed during and immediately after the intravenous administration of the ascitic fluid, nor can it therefore be the possible cause of the fatal outcome. On the contrary, it could be even asserted that it contributed its own towards the survival of these patients from the immediate dangers of both the operation itself as well as the collapsed state with which they went to the operating room.

CRITERIA AND PRECAUTIONS OBSERVED. Cognizant of the possible untoward and even fatal effects of this procedure, we observed strict precautions in the selection of ascitic fluids. The only kinds of fluids suitable for such intravenous use are those having the character of transudates; exudates being absolutely contraindicated even if these were apparently sterile. We obtained the fluids following the routinary procedures for an aseptic operation, collecting it into sterile bottles. In this regard, some workers recommend the use of citrate. In our cases, we did not feel this to be very necessary, inasmuch as, after all, these fluids do not tend to coagulate spontaneously. Our sources were cirrhotic cases, cardiac cases, hypoproteinemic cases, both from undernutrition as well as of nephrotic nature.

A small sample was collected into a separate container for complete laboratory analysis. A simple Rivalta test sometimes was not sufficient, in view of false reactions for exudate even if the fluid was a real transudate. This was particularly true in those in which the fluid had been in the body cavity for a sufficient length of time, allowing a good proportion of the water to be absorbed and leaving a good percentage of proteins in a relatively small liquid, thus sufficient to give reactions for exudate by the method of Rivalta. Such fluids would have been discarded if not further studied. And, these are precisely the kind fluids which serve best our purpose, in intravenous injection—transudates with high protein content.

Total proteins were determined by either Esbach's simple technic or by the more elaborate procedures for total proteins in the blood. Then, cell counts and bacteriological studies were made. Needless to say, fluids yielding positive cultures, especially for spore-forming bacteria, were immediately discarded. On the other hand, a total cell count of 10 per cu. mm. was taken as the standard for transudate fluids.

Then, after it had passed the above criteria, the fluid was finally filtered through a Seitz filter into sterile containers and then heated in a water bath at 60° C. for 2 hours for 3 consecutive days. Thus, the fluid becomes ready then for either homologous or heterologous intravenous transfusion. If not readily used, it could be kept at refrigerator temperature preferably not above 12° C.

Comments and Summary. We repeat, these trials in human cases are the first of their kind in the Philippines. It was only because of the peculiarly unusual predicament in which we found ourselves during those three years of Japanese occupation that we felt courageous enough to resort to this measure in human cases, as a possible last remedy, in the absence of other fluids that are more highly recommended for parenteral use.

Fortunately, not only did we verify the few successful results that we were then aware of, not on experimental animals this time but in human patients, but also we realized the fact that ascitic fluid for intra-

venous use seems to have its rightful place in our medical armamentarium.

In all our cases, except in Case 3, no untoward effects were observed. Even in this case, the slight unpleasant side effects could easily be explained by the rapidity of its administration, an impression that was later verified in the next doses given more carefully and at a slower rate. The fatal outcome of the other cases operated upon, likewise, could not be ascribed to the venoclysis of ascitic fluid during the operations, as those patients survived the operations and succumbed several days later to varied conditions.

In Case 3, the unusual beneficial effects of ascitic fluid in nephrotic syndrome was evidenced by the marked, immediate and prolonged diuresis that ensued. A possible explanation could be the increase in the osmotic pressure in the blood, due to the higher protein content of the ascitic fluid, similar to that said to be produced by the use of acacia solution or lyophile serum in such cases of hypoproteinemia.

In cases of shock, as typified by Case 4, ascitic fluid could serve as a safe and efficient substitute for other parenteral fluids, and could thus be a life saving measure.

It is clear, therefore, that the use of human ascitic fluid intravenously is a safe procedure, provided that proper criteria are followed in the selection of the suitable fluids and certain precautions observed in its use. From the therapeutic results we observed in the cases here reported, we believe this subject merits consideration and further investigation. After all, one of the tendencies of recent advances and discoveries is the detection of the therapeutic potentialities of the very same products or by-products of the human body.

The junior authors of this paper offer this humble work as a tribute to the senior author, Dr. Ricardo Molina, whom we lost during the battle for the liberation of Manila. His guidance and inspiring courage have been the encouraging spirit that enabled us to undertake these trying experiences. Acknowledgement is also made to Dr. E. Medina Cue, Chief of the U.S.T. Clinical Laboratory, who was solely responsible for the selection, laboratory analysis and preparation of the ascitic fluids that we used in our cases.

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RENAL EXCRETORY FUNCTION AND DIET IN DIABETES INSIPIDUS

By Samuel B. Beaser, M.D.

(Assistant in Medicine, Harvard Medical School, and head of the Diabetic Clinic, Beth Israel Hospital, Boston, Mass., on leave of absence in the U. S. Army.)

The primary dysfunction in diabetes insipidus is a deficiency in the supply of the antidiuretic hormone of the posterior pituitary gland, resulting in deficient reabsorption of water by the distal renal tubules[50] and thereby producing polyuria and polydypsia. In the diabetes insipidus of the dog, Winter, Ingram and Eaton[51] have shown that the poluria varies directly with the total daily osmillimolar* excretion of NaCl and nitrogen (calculated as urea) of the urine. In man, likewise, these two constituents form the bulk of the various solids of the urine both in the normal[24] and in the diabetic insipidus patient[20]; accordingly, a similar simple quantitative relationship might conceivably exist in the human also. This investigation was undertaken in order to clarify this point by a study of the renal excretory function of human diabetes insipidus. For this purpose data were utilized both from our patient and from eight other cases culled from a review of the literature on diabetes insipidus.[3,20,30,43,46]

Methods. Our patient was placed on a succession of measured diets, all equicaloric (about 2800 Calories) and varying in a calculated manner with regard to salt and/or protein. This patient as well as those of the other authors were allowed water ad libitum throughout all dietary regimes. The daily urines were collected from 7 A. M. to 7 A. M., the patient eating breakfast shortly after that hour. Total urine chloride was performed by the method of McLean and Selling[26] (expressed as grams of NaCl per liter) and total urine nitrogen by the micro-Kjeldahl method. In the calculation of milliequivalents of nitrogen in the urine, all the nitrogen was assumed to be in the form of urea,† following the method of Winter et al.[51] This method of calculation of nitrogen excretion was followed also in recalculating the results of the other authors. In the conversion of milliequivalents to osmillimols, no change was necessary in the case of nitrogen; the value of salt in milliequivalents was simply multiplied by two.

The cases of the other authors had had similar studies performed with diets varying in each patient both as to salt and protein intake so as to provide a range of daily excretion of nitrogen and salt from 200 to 700 osmillimols. The urine specimens had been studied in essentially the same way.

Plan of Study. Our patient was placed on dietary regimes for five successive periods as noted in Table 1. The salt supplement to the diet was administered dissolved in fruit juice. In order to achieve an arbitrary total of 140 gm. of protein a day most conveniently, supplements of gelatin powder (Knox gelatin: 80% Protein) were administered in fruit juice. On the last day of period 5 (all periods were four days in length), the patient experienced anorexia, so that a small portion of the diet was not ingested.

The 8 patients of the other authors had similarly been placed on diets varying in protein and salt content, but not in the same calculated succession. These patients were either on a single type of regime for longer periods of time or simply on high or low salt or protein days. They all had in common however a number of days with sufficiently wide variations in total daily osmillimolar excretion of urinary producers.

Results. Three characteristic deviations from normal renal function, observed in isolated cases previously,[30,46] are here (Table 2) delineated more quantitatively: *A. The Low Average Urine Concentration*;

* Osmillimols = 2 × millimols NaCl + millimols urea.

† This method introduced a small error, particularly at low protein diets where the proportion of the nitrogenous excretion products of higher molecular weight is increased.[13,34,45]

B. The Low Maximum Urine Concentration; C. The Low Reserve Urine Concentrating Power. As a conclusive demonstration of the fixed characteristic of the urine of diabetes insipidus, the normal is seen to have 42 times greater range of concentrating power than these patients. These conclusions can be applied equally well to the nitrogen and salt concentrating powers separately. It may also be noted that all the urine concentrations were reduced uniformly to about the same low range without a gradual transition from the normal.

For all the 9 diabetic insipidus patients the relationship between daily urine volume and daily output of urea and NaCl in osmillimols could be expressed with sufficient accuracy by a straight line. Fig. 1 shows a typical example from the data* in 1 case. The renal excretion curve of each patient, individually characteristic both as to slope and position in relation to the coordinates of the graph, could therefore be described mathematically by the formula:

$$UV = UV_o + S \cdot O_{sm}$$

where UV is the daily urine output in liters, S the slope of the curve and Osm., the total daily renal excretion of nitrogen (as urea) and NaCl in osmillimols. UV_o is the intercept constant of the line with the UV axis. These constants are shown in Table 3.

As a consequence of the above formulation, 2 additional characteristics of the renal function in diabetes insipidus emerge:

TABLE 1.—DIETARY REGIMEN FOR FIVE SUCCESSIVE PERIODS

Diet Period Number	Total Protein Intake Gm.	Food Protein Intake Gm.	Gelatin Protein Added Gm.	Total NaCl Intake Gm.	Food NaCl Intake Gm.	NaCl Added Gm.
I.	85	85	0	6.5	6.5	0
II.	31	31	0	6.5	1.2	4.3
III.	31	31	0	1.2	1.2	0
IV.	140	85	55	1.2	1.2	0
V.	140	85	55	16.5	6.5	10

TABLE 2.—VARIATIONS IN URINE CONCENTRATIONS AND VOLUME*

Component	Diabetic Insipidus Patients† Range	Average	Normal‡
Nitrogen (as urea)	Max. 29–66	46.9	875 (Chaussin[8])
	Min. 9–34	17.2	162 (Folin[15])
	Diff. 17.5–41.0	29.7	713
NaCl	Max. 21–175	65.9	745 (Chaussin)
	Min. 1.4–80.0	23.2	146 (Folin)
	Diff. 3.5–95.0	42.7	599
Total N plus NaCl	Max. 56.8–215.0	91.6	1250 (Chaussin)
	Min. 36–165§	72.3§	440 (Folin)
	Diff. 5–50	19.3	810
Urine Volume	Max. 5.5–17.5	10.8	
	Min. 1.6–6.2	3.6	
	Diff. 3.1–14.0	7.2	

Comparative table of urine volume and concentration characteristics of normal and 9 diabetic insipidus patients (including the recalculated data from 8 cases of other authors[3,20,30,43,46]).

* The urine volume is expressed in liters, the remaining components as osmillimols per liter.

† The diabetic insipidus patients had been on diets varying considerably but only a few approached in severity the stress under which the maximum values for the normal had been obtained.

‡ The data for the normal human at maximal dietary stress were secured from Chaussin[8] as a resultant of several experiments on one patient and at normal dietary stress from Folin[15] as an average derived from 6 patients.

§ These concentrations were secured from Table 3 C. The figures for the range were based upon the values of the individual patients in each case, maximum, minimum and differences.

* The relationship was not as smooth when calculated in terms of milliequivalents. Osmotically, nitrogen and salt are of equal importance in the usual range of diets and renal excretion.

D. The Increment of Urine Necessary to Excrete Each Additional Osmillimol of Salt or Urea is Constant and Characteristic for Each Patient ("S"); and E. In a Given Diabetic Insipidus Patient, the Urine Concentration Expressed as Osmillimols Per Liter Increases as the Total Osmillimolar Excretion Rate Increases; in Different Patients, The Rate of Change in the Total Osmillimolar Excretion Rate is the Greater the Greater the UV_o of the Given Patient. Inspection of the actual data of these cases confirmed the latter statement in that, as the patients changed from lower to higher daily total excretion rates, those patients with the greater UV_o showed increasing

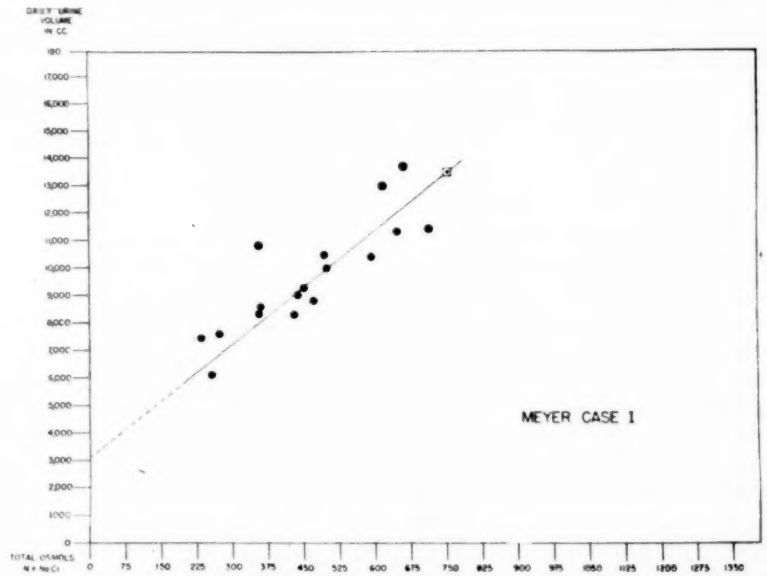

FIG. 1.—From a case of human diabetes insipidus (Meyer[30] Case 1), data recalculated. The relationship between urine volume and total daily combined output of nitrogen and NaCl in osmillimols (labelled osmols) on varying diets. Square symbol represents output on unrestricted diet. The dotted line extension was an extrapolation. This curve was drawn by visual estimation. For constants according to the method of least squares, see Table 3.

TABLE 3.—EFFECT OF DIETARY RESTRICTION

Diet.		Cases								
		Meyer V	Allen IV	Beaser	Meyer II	Tallqvist	Stenstrom	K&M	Meyer I	Allen III
A. Unrestricted	UV	5.5	8.0	10.5	10.5	10.0	11.5	7.5	13.5	10.5
B. Normal (Folin)	UV	2.7	6.7	7.3	5.2	7.0	9.7	6.6	9.3	12.2
	Osm.	440	440	440	440	440	440	440	440	440
C. Normal	UV	2.8	6.8	7.2	5.35	7.0	10.0	6.7	10.1	11.9
(calculated)	Osm.	462	510	434	462	443	462	462	498	427
D. Low Salt Ave.	UV	1.8	5.2	4.4	4.0	4.5	6.8	5.5	7.3	8.7
Protein	Osm.	284	332	256	284	265	284	284	310	249
E. Low Salt Low	UV	1.3	3.7	3.0	3.25	3.5	5.3	5.0	6.1	7.2
Protein Diet A	Osm.	196	222	181	196	190	196	196	209	175
F. Low Salt Low	UV	0.9	2.45	2.5	2.7	2.8	4.3	4.6	5.2	6.5
Protein Diet B	Osm.	139	139	139	139	139	139	139	139	139
G. Weight in Kgm.		72	90	61	72	65	72	72	81	60
H. Slope, S		0.0036	0.0122	0.0148	0.0074	0.0127	0.0154	0.0084	0.0128	0.015
I. Intercept, UV_0		1.61	1.18	1.04	2.16	1.02	2.50	2.94	3.78	4.48
J. Standard Error of UV		0.51	0.48	1.08	0.90	0.42	1.23	0.56	1.23	2.00
K. Maximum	+	1.0	0.78	1.9	2.12	0.8	2.1	1.3	2.8	4.8
Differences of UV	−	0.7	1.0	2.24	1.53	0.7	1.95	1.1	1.5	3.2

urine concentrations whereas those with low UV showed relatively constant urine concentrations.

As a further consequence of this formulation, we must revise our usual definition of severity in this disease, namely: the urine volume excreted on a regular diet. Instead, we may now estimate or calculate the severity of the diabetic insipidus renal function by the area beneath the patient's renal excretory curve or define its deviation from normal by the ratio between that area and that smaller area beneath the relatively constant normal human curve.

patient has been rearranged to illustrate the point that the greatest reduction of urine volume was attainable only when *both* dietary components were reduced to low levels* (protein, 1.49 grams per Kgm. body weight and salt, 1.2 grams per day).

In Table 3, this conclusion is confirmed for all the patients studied. The more moderately restricted diet (A) was able to reduce the urine volumes of 5 of the 9 patients to the relatively convenient zone below 3700 cubic centimeters. It is seen that the likelihood of ameliorating the polyuria by dietary restriction is the

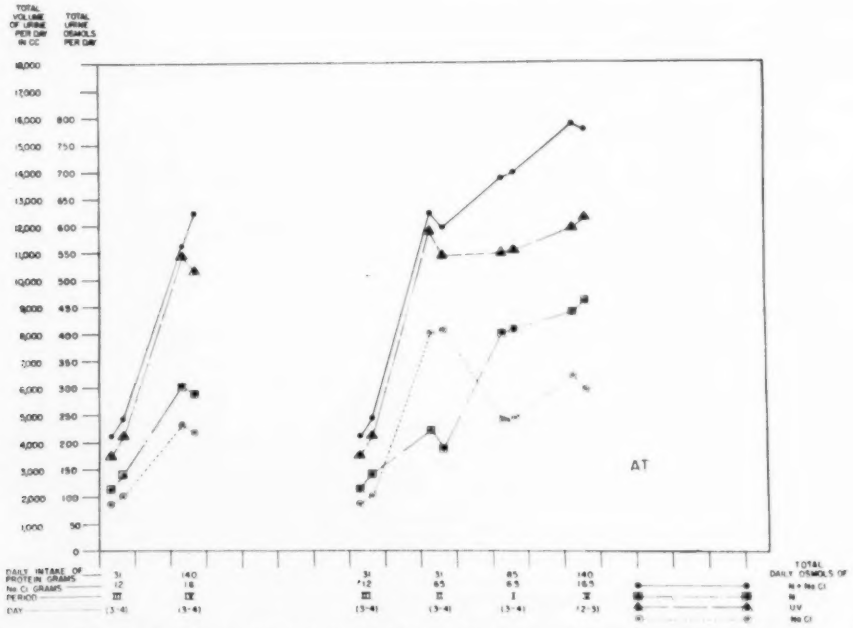

FIG. 2.—From our patient with diabetes insipidus. Data from the last two days of the diet periods of Table 1 rearranged to illustrate the effect upon urine volume and rate of excretion of salt and/or nitrogen, in osmillimols (labelled osmols), of variation in the quantity of dietary protein and salt, in that order.

No simple mathematical relationship could be observed between the *total* daily excretion of *either* nitrogen or salt and either diet or urine volume. However, the relationship between dietary intake and urinary output can now be seen with clarity. In Fig. 2, the data from our

greater the smaller the UV_o. Furthermore, it is of interest that the diabetic insipidus patients' desire for salt and protein when allowed a diet of choice cannot be relied upon to adjust itself to the concentration defect (unlike thirst). This is not related to the weight of the patients.

* That these conclusions were not due to the short duration of the diet periods was shown by the failure of a 15 day trial of a normal protein, low salt regime to reduce the urine volume to its lowest level.

Discussion. In defining more quantitatively the range of renal concentrating function in these patients with diabetes insipidus, it is worthy of note that all have been reduced to a relatively uniform low level, with none in the wide transitional area. In the light of the increasing evidence for the large reserve capacity of the antidiuretic mechanism of the posterior pituitary gland,[35,37] this would seem to indicate that the disease represents practically complete decompensation of this mechanism. The importance of this concept is that it would classify the remaining excretory and concentrating characteristics of a given diabetic insipidus patient as largely residual and extra-pituitary in origin.

While the normal human evinces a slight tendency to constancy of urinary concentration on various diets,[1] this becomes pronounced when the kidney's concentrating powers are taxed.[8] This invariability of urinary concentration in the diabetic insipidus patient then seems to be an exaggeration of a normal tendency of the kidney made obligatory by the low concentrating ability and low reserve, so that it works at practically its maximum (although low) rate at all times.

The straight line relationship observed between urine volume and osmotic output testifies to the exact correlation between water supply and requirements, since the diabetic insipidus patient cannot efficiently dispose of excess water as can the normal.[36] In view of the fact that thirst was the sole regulating mechanism of supply here, this further confirms the close interrelationship between thirst and osmotic balance of the body,[16] represented here by osmotic excretory needs.

With the all or none concept of the pathogenesis of diabetes insipidus in mind, we may speculate regarding the significance of the mathematical constants defining the renal excretory pattern of the individual patient. We might conceive of "S" as the basic distal tubular concentrating pattern of the patient, the individual characteristic features of which were brought to light only in the absence (or deficiency)* of distal tubular water reabsorption. The variable UV_o which elevates the curve of the diabetic insipidus patient by comparison with the normal is equivalent to a constant excess of water requirement (thirst), independent of dietary load, and necessary to satisfy some set of circumstances associated with renal function and endogenous in origin. It probably is related to the other known renal abnormality of this disease, increased salt reabsorption by the proximal renal tubules.[36,37] This, if continued, would tend to produce a more hypertonic blood (with respect to NaCl); the latter can be recognized as a most important physiological stimulus to increased thirst,[16] in this case one which would be rather precisely geared (by a common origin) to the polyuria which it would be called upon to satisfy.†

The renal excretory curve may prove to be a useful tool for the study of this disease and the evaluation of therapeutic procedures; however, of immediate interest is the light it throws on dietary therapy. Efforts to control the polyuria by water deprivation accomplish little except dehydration and needless suffering.[10,25,48] By contrast, it has been repeatedly observed that some restriction of dietary salt and protein has a beneficial effect.[14,30,31,43,46] Some observers attained therapeutically incomplete results due to inadequate restriction of both constituents[20] or due to the curtailment of only one of them.[25] Allen, after a careful study, concluded that both had to be restricted radically to

* If, as some seem to assert,[22] the diabetic insipidus patient has normal kidney excretory function but a pathologically increased thirst, he would have a curve of normal slope but elevated above the abscissa.[34]

† It is tempting to speculate that a variable portion of the increased salt reabsorption may be due to an unopposed adrenal cortical effect occurring as a release phenomenon in the absence or diminution of the effect of its antagonist, posterior pituitary gland. Under those circumstances, UVo should then be a function of the adrenal activity of the patient and should vary independently of the "S", as it does.

produce real benefit, that the effects were independent of caloric intake, and that patients could be so regulated for long periods of time with no deleterious effects.[3] Because of unpredictable variation from patient to patient in the degree of therapeutic benefit attained,[3,30] an understandable confusion ensued, resulting in the necessary and that the degree of success attainable is both variable and predictable from the "S" and "UV_o". Moreover, the importance of reducing protein intake calculated on a weight basis would obviously be greater the heavier the patient. In the practical management of a given case, determination of the excretory curve

TABLE 4.—LOW SALT, LOW PROTEIN DIET (A)*

	Contents in Grams			
	Protein	Fat	Carbohydrate	Salt
Breakfast:				
200 gms. Orange juice	1	0	24	.016
15 gms. Dry cereal	1.5	0	7.5	.017
30 gms. Toast	2	0	16	.130
20 gms. Butter—salt free	0	16	0	.004
40 gms. Jelly—2 tablespoons	0	0	26	0.0
200 gms. Milk	6	8	10	.360
50 gms. Cream	1.5	10	2	.065
20 gms. Sugar—1 tablespoon	0	0	20	0.0
Dinner:				
45 gms. Roast beef, medium fat	12.1	8	0	.076
100 gms. Baked sweet potato	1.8	0	28	.060
100 gms. Asparagus	1.6	0	3	.060
100 gms. Sliced tomato	1.0	0	4	.060
30 gms. Mayonnaise—2 tablespoons	0	22.5	0	.128
30 gms. Bread	2	0	16	.130
20 gms. Butter—salt free	0	16	0	.004
40 gms. Jelly	0	0	26	0.0
100 gms. Banana	1.2	0	23	.206
50 gms. Cream	1.5	10	2	.065
20 gms. Sugar	0	0	20	0.0
Supper:				
100 gms. Potato	2.0	0	19	.060
100 gms. Braised celery	1.3	0	4	.260
100 gms. Carrots	1.1	0	9	.050
100 gms. Lettuce	1.2	0	3	.120
30 gms. Mayonnaise	0.0	22.5	0	.128
100 gms. Cherries	1.1	0	15	.021
30 gms. Bread	.2	0	16	.130
30 gms. Butter—salt free	0	20	0	.006
40 gms. Jelly	0	0	26	0.0
50 gms. Cream	1.5	10	2	.065
20 gms. Sugar	0	0	20	0.0
Totals:	43.4	143	341.5	2.221

General rules for a low salt diet: 1. All foods to be prepared without condiments. 2. No salt to be used at the table. 3. Use salt free butter. 4. Do not use commercially canned foods unless labeled salt free. 5. Avoid the use of foods of high salt content such as ham, pork, bacon, all nuts, salt water fish, and cheese.

* From Army Manual T. M. 8–500.

present day teachings which disregard or minimize the need for the reduction of the protein intake.[4,7,9,32] Instead, the entire stress is laid upon replacement therapy which is now more easily administered than previously.[6,17]

The present study has shown that restriction of both dietary constituents is is an unnecessary refinement, for which can be substituted therapeutic trial of a diet. Diet A (Table 4) is attractive and convenient, while Diet B (Table 5), less appetizing but of greater potential benefit, satisfies the minimum human requirements.[2,3,18,23,27,39,42,44]

The distribution as well as the total

amount of ingested food is of practical importance. In the diabetic insipidus as in the normal it is in the first several hours after a meal that the major portion of the nitrogen[30] and salt [11,25,49] excretion of that meal occurs, in addition to a concomitant increase in the glomerular filtration rate.[38] In the normal human such excretion does not carry over into the sleeping hours except when on excessive intakes, under which circumstances both salt[8] and nitrogen[24,38] excretion persist into the night, with accompanying nocturia. In the diabetic insipidus with a tendency to nocturnal polyuria on a normal diet, it would be highly expedient to avoid both the accumulative and immediate effects of diet by a total reduction of the intake of salt and protein and their redistribution to the breakfast and noon meals.

In order to draw general conclusions as to the applicability of dietary control in this disease, information regarding the frequency distribution of cases by severity would be desirable. The latter, based solely on urine volume on an unrestricted diet, can be estimated roughly from 2 large series of cases in the literature[19,35] (Table 6). Of those patients, over 50% had an output of less than 8 liters per day. Since dietary regulation proved of great benefit even to the 8 patients (Table 3) with a daily urine output exceeding 8 liters, it would indicate a large sphere of usefulness for this type of treatment when used alone in diabetes insipidus.

TABLE 5.—LOW SALT, LOW PROTEIN DIET (B)*

	Contents in Grams			
	Protein	Fat	Carbohydrate	Salt
Breakfast:				
200 gms. Orange juice	1	0	26	.01
30 gms. Dry cereal	2	0	24	.03
40 gms. Jelly	0	0	26	0.0
30 gms. Toast	2.5	0	16	.13
20 gms. Butter—salt free	0	16	0	.004
200 gms. Milk	6	8	10	.36
50 gms. Cream	1.5	10	2	.039
30 gms. Sugar	0	0	30	0.0
Ad Lib. Black coffee	0	0	0	0.0
Dinner:				
50 gms. Lamb chop	10	15	0	.15
100 gms. Carrots	1	0	9	.05
100 gms. Lettuce and tomato	1	0	3	.09
33 gms. Mayonnaise	0	25	0	.12
30 gms. Bread	2.5	0	16	.13
20 gms. Butter—salt free	0	16	0	.004
40 gms. Jelly	0	0	26	0.0
100 gms. Pineapple ice	0	0	27	0.0
50 gms. Cream	1.5	10	2	.039
30 gms. Sugar	0	0	30	0.0
Ad Lib. Black coffee	0	0	0	0.0
Supper:				
100 gms. String beans	1	0	3	.04
100 gms. Squash	0.5	0	4	.01
75 gms. Coleslaw	1	0	2	.03
33 gms. Mayonnaise	0	25	0	.12
30 gms. Bread	2.5	0	16	.13
20 gms. Butter—salt free	0	16	0	.004
40 gms. Jelly	0	0	26	0.0
100 gms. Grapefruit	0.5	0	10	.008
50 gms. Cream	1.5	10	2	.039
30 gms. Sugar	0	0	30	0.0
Totals:	36	151	340	1.537

(Total Calories: 2863)

* From Army Manual T. M. 8–500.

With respect to replacement therapy, nasal pituitrin may be ineffective or only partially effective[28,41] due to local absorption difficulties or to the severity of the disease. In either event, diet may be adequate to replace it entirely or to render it effective. Even inadequate dietary control such as salt restriction alone has been tried and found useful as an adjunct to the quick acting parenteral preparations.[21,29] The newer slowly acting preparations, now being used more widely, have been most useful in the more severe cases, but carry with them the possibility of complications such as menorrhagia[47] or water intoxication.[12,47] Here, too, diet would be of value both in ameliorating the polyuria and decreasing the dosage or frequency of administration of therapy. Certainly, dietary control is worthy of a trial in every case, with or without posterior pituitary extract, according to the severity of the disease.

Summary. 1. The low concentrating activity and reserve power of the diabetic insipidus kidney of man was quantitatively demonstrated.

2. A straight line relationship was noted between urine volume and the total excreted quantities of salt and nitrogen expressed in osmillimols.

3. This curve of renal excretion was found to be characteristic for each patient and was defined mathematically.

4. A new quantitative definition of severity in this disease is proposed in terms of renal excretory dysfunction.

5. The renal excretory curve of a diabetic insipidus patient provides a quantitative method of measuring the effect to be expected from dietary restriction or other procedures.

6. It has been demonstrated that maximum restriction of *both* salt and protein of the diet is necessary in order to attain maximum therapeutic benefit.

TABLE 6.—DISTRIBUTION OF CASES OF DIABETES INSIPIDUS ON THE BASIS OF "SEVERITY" *

Author	Urine Volume: Below 8 Liters		8–12 Liters		Over 12 Liters	
	Number	%	Number	%	Number	%
Rowntree[35]	19	34.5	21	38.2	15	27.3
Jones[19]	31	76	5	10	6	14
Composite Total . .	50	51.5	26	27	21	21.5

* Severity in this table refers to the urine volume on an unrestricted diet.

The effect of dietary restriction upon urinary output of the 9 patients with diabetes insipidus. The values for urine output were derived from the excretion curves, the constants of which (H, I, J, K) were calculated by the method of least squares. Patients arranged in order, reading from left to right, of the lowest to the highest urine volumes attained at the lowest diet (F). Urine output, UV, was expressed as liters. Osm. indicates the osmillimols of nitrogen plus NaCl excreted at the eventually to be expected equilibria of the patients at the respective diets. Normal (Folin) diet was derived from Folin's "average" diet.[18] Normal (calculated) diet was based upon 1.5 grams per Kgm. of body weight of protein and 8 grams of salt daily.[8] Low salt—low protein diets refer respectively to Tables 4 (low, definitely adequate daily protein)[40] and 5 (minimum, daily protein).[39] Where the author did not furnish the patient's weight, it was assumed to be 72 Kilograms.

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OBSERVATIONS ON THE TREATMENT OF CARCINOMA OF THE PROSTATE BY ORCHIDECTOMY

By Ernest K. Landsteiner, M.D.
INSTRUCTOR IN GENITOURINARY SURGERY, HARVARD MEDICAL SCHOOL; JUNIOR ASSOCIATE IN GENITOURINARY SURGERY, PETER BENT BRIGHAM HOSPITAL
ASSISTANT IN SURGERY, HARVARD MEDICAL SCHOOL
AND
Hathorn P. Brown, M.D.
BOSTON, MASSACHUSETTS

(From the Urological Clinic of the Peter Bent Brigham Hospital)

The treatment of advanced carcinoma of the prostate by androgen reduction through orchidectomy or the administration of estrogens as suggested by Huggins[5] has stimulated much discussion regarding the results to be achieved by this form of therapy. During the past 4 years the clinical as well as the endocrine and chemical aspects of such therapy have been energetically investigated. The following conclusions are generally agreed upon: 1. Androgen reduction offers the best prospect for the relief of symptoms due to secondary deposits of prostatic carcinoma. 2. A significant number of patients are dramatically improved while many others obtain partial relief. 3. Some patients show little or no improvement, the downhill course of their disease being unaffected by any form of endocrine change.

At present, three methods of endocrine control are in use: Surgical castration, estrogen therapy, and a combination of these. There is as yet no unanimity of opinion regarding the exact indications for the use of any one of these methods. This is explained largely because there has not been sufficient time in which to observe and compare a sufficient number of patients treated by each method. Carcinoma of the prostate often runs a long and unpredictable course and this adds greatly to the difficulty of properly evaluating any type of treatment. An added difficulty is the lack of knowledge regarding the endocrine and metabolic changes brought about by these forms of therapy. Further evidence regarding the problem will depend, therefore, on endocrine studies and continued clinical evaluation of patients treated by these methods.

In this report, we discuss the clinical findings of patients with carcinoma of the prostate treated exclusively by orchidectomy during the past 4 years. Additional surgical procedures for the relief of urinary symptoms were also carried out whenever necessary. Thirty-five patients have been studied and followed for from 6 months to 4 years, over half of them for more than 2 years. The patients varied in age from 53 to 87, the average being 70 years. Of the 35 cases, 20 had a positive microscopic diagnosis of carcinoma of the prostate, while in the remaining 15 cases the diagnosis was made by physical findings, elevated acid phosphatase, and Roentgen ray evidence of bony metastases. Of the 35 cases, 23 showed evidence of metastases either by Roentgen ray or acid phosphatase or both, while 12 had no evidence of metastases. Of the 23 with metastases, 9 died within one year after orchidectomy, two within 2 years and one 28 months after orchidectomy; 11 are living and relatively asymptomatic (8 to 25 months after operation). Of the 12 cases without evidence of metastases, 5 are living (6 to 30 months after operation), 3 died within the first year, one died in the second year, and 3 died after three years.

Thirty-one urologic operative procedures other than orchidectomy were performed in 22 of these cases. Cystotomy by suprapubic punch for the purpose of placing the bladder on constant drainage was done in 11 patients who were admitted

to the hospital in acute retention. Of this group one patient died of pneumonia after orchidectomy before any further procedure to free the bladder outlet could be carried out. Three patients were able to void after orchidectomy and the suprapubic opening could be dispensed with. One patient had a partial perineal prostatectomy to free the outlet of the bladder. The remaining 6 patients subsequently had transurethral resections.

Six patients had had a suprapubic prostatectomy prior to the development of carcinoma and 2 of these required further removal of tissue (transurethral resection) to free the outlet of the bladder. In 7 patients the prostate was explored through the perineum; one total and 3 partial prostatectomies were performed in 4 patients prior to orchidectomy, and 3 had a biopsy of the prostate through the perineum. Transurethral resection was carried out in a total of 10 cases. Three of these required a second transurethral resection at a later date. Suprapubic prostatectomy was carried out in 2 of the patients.

An analysis of the cases and the results of orchidectomy has been made from the following five aspects: 1. Relief of pain due to metastases; 2. Improvement in well-being (appetite, weight, etc.); 3. Roentgen ray changes in the metastases; 4. Improvement in urinary symptoms; 5. Changes in acid phosphatase.

1. Of the patients having metastases, approximately two-thirds experienced moderate to severe pain preoperatively. After removal of the testes dramatic and marked relief of pain was experienced by one half the patients and the other one-half showed slight to moderate improvement. No patient of the group with metastases failed to show some improvement, temporary though it may have been in some cases. In practically all of the cases surgical castration was followed by amelioration of symptoms within 48 hours. This rapid response suggests that pain as such is more likely due to pressure on or actual involvement of nerves by carcinoma (usually in lymphatics or lymph nodes) rather than by intraosseous growth which will show no detectable change by Roentgen ray in so short a time. By way of illustration, the only case showing structural deformity of a vertebra due to carcinomatous invasion received only minimal relief from orchidectomy. One must assume that in this case pain was caused by vertebral collapse rather than by nerve involvement outside the spine. Little improvement, therefore, can be expected in cases in which the bony metastases destroy the normal contour of the vertebral column. On the other hand, where pain is caused by peripheral nerve involvement, one may expect relief in a majority of the cases.

Along with other observers[8], we have found that patients who were bedridden and required large doses of opiates were able, in several instances, to resume their former occupations and no longer required sedation.

2. As might be expected, improvement in well-being and appetite paralleled relief of pain in almost all instances. There were also several cases, not suffering from pain and with no evident metastases, who showed an increase in weight, appetite, and general well-being. Improvement in well-being may be very rapid and dramatic as illustrated by the following case:

Case Report. CASE 1. The patient, a 65-year-old Italian longshoreman, entered the hospital in a very cachectic condition, having lost over 20 pounds in 6 months. He had suffered marked fatigability, anorexia, nausea, vomiting, and pain in the back and both legs. He had no urinary symptoms except slight nocturia.

Physical examination revealed a very pale, emaciated man who showed marked wasting of the extremities. There were no abdominal masses or lymphadenopathy. Rectal examination showed the prostate markedly enlarged with definite evidence of malignancy. Acid phosphatase determination was 12 units. Roentgen rays revealed osteoplastic metastases in practically every bone in the body, including the skull and ribs. A severe secondary anemia was also present.

Bilateral orchidectomy was performed and was followed by marked diminution in pain and cessation of nausea and vomiting within 48 hours. Acid phosphatase was 6 units on the eighth postoperative day. He was discharged much improved on the eleventh postoperative day. At the end of 6 months the patient had returned to limited work, had gained 22 pounds and his red blood count had become normal. At the end of one year he was feeling extremely well, was still gaining weight and his acid phosphatase was reduced to 1 unit. Fifteen months after orchidectomy he was readmitted to the hospital because of recurrence of severe pain in the back and both legs for two weeks. He also had pain in the right elbow and sternum. The patient had lost 10 pounds in weight and the acid phosphatase was re-elevated to 6 units. He was treated with large doses of stilbesterol—up to 5 mg. daily—but did not respond in any way, nor was there any relief of pain. His general condition became steadily worse and he died one month later.

This case further illustrates the symptomatic relapse which may occur at variable periods after orchidectomy. After relapse, these patients, as a rule, are little affected by therapy with estrogenic compounds and go rapidly downhill.

3. In our series of 35 cases, 18 had evidence of metastases as seen by Roentgen ray. Examination of the chest, spine and pelvis was carried out in each patient and other areas were examined whenever indicated. Osteoplastic metastases were observed in the spine and pelvis 18 times, ribs 9 times, pleura twice and lung fields twice. Repeated Roentgen ray examinations were possible in 16 of these patients at various intervals after bilateral orchidectomy.

An exact evaluation of the changes occurring in the Roentgen ray appearance of metastatic lesions is extremely difficult and requires that great care be taken both in the preparation and the interpretation of the films. They must be made under uniform conditions on repeated examinations in order to allow accurate comparison of the size, number and density of metastases. Careful comparison of both pre- and post-operative films must always be made, particularly when it appears that new bony metastases have occurred since orchidectomy. Often review of the same areas in the preoperative film will disclose the presence of previously overlooked metastatic areas which have increased in density and thus first been noticed on the postoperative films.

In the bones there were no constant changes which could be interpreted as signifying regression. Most frequently the osteoplastic metastases became more calcified and appeared more discrete. A number of times, however, the lesions became larger as well as more numerous and widespread. In a few cases there was no significant change, and two cases only showed decreased density of the osteoplastic lesions with a partial restoration of normal bone architecture.

In one of these there was a remarkable diminution in the size of the metastases, almost all of the neoplastic areas being replaced by normal bone. This change had not occurred by one month after orchidectomy, but was noted on the second examination more than one year after operation. During this time the patient's clinical course has been extremely satisfactory. He has experienced complete relief from pain, has gained weight and has shown marked improvement in urinary function.

A very favorable change in the Roentgen ray appearance of metastases occurred in one of 2 patients having metastases to the lung fields. Three months after bilateral orchidectomy these secondary deposits were greatly diminished in size and the lungs appeared remarkably improved. The other patient showed a similar but much less striking change. Of the 2 patients with metastases to the pleura, one was unchanged after operation, and the other showed diminution in size of the metastatic nodules.

Several of the patients who showed a progression of metastases by Roentgen ray did so in spite of marked clinical improvement. One patient, previously free

of metastases by Roentgen ray, developed them throughout the spine and ribs three months postoperatively. He died shortly thereafter.

In general, it is our feeling that the Roentgen ray changes in bony metastases cannot be interpreted as indicating regression except in rare cases in which normal bone architecture is restored after orchidectomy. There is little in the usual Roentgen ray response to suggest the extent or duration of clinical improvement. However, in those cases in which there was partial restoration of normal bone architecture or clearing of metastases from the lung fields, there was also very satisfactory clinical improvement.[4]

4. There have been several reports in the literature stating that decrease in the size of the carcinomatous prostate and improvement of urinary function are to be expected following androgen depression therapy.[1,3] It has been our experience that this favorable effect on urination cannot be expected in the majority of cases. Although a decrease in the size and softening of the original lesion was observed in about one-third of the patients treated, only 5 showed a resulting improvement of urinary function and diminished residual urine. Three of these had been placed on suprapubic drainage because of severe retention prior to orchidectomy, and in these the retention was relieved, permitting withdrawal of the catheter and complete healing of the suprapubic sinus. Two others showed a marked reduction in residual urine soon after orchidectomy. In all of these cases the prostate showed diminution in size and became softer.

A case in which local extension of the lesion showed diminution in size is of particular interest.

Case 2. The patient, a 70-year-old expugilist, entered the hospital because of frequency, burning on urination, chills, fever, nausea, vomiting and pain in the left flank for one week. He had been treated at home with sulfathiazole, 3 gm. daily, since the onset of his illness without showing any improvement. Four years previously at this hospital he had had a suprapubic prostatectomy for benign prostatic hypertrophy. At the present examination there were signs consistent with a blocked left kidney. The kidney was enlarged, tender, and showed no excretion on an intravenous urogram. Rectal examination revealed a markedly enlarged, stony-hard, nodular prostate with extension of malignancy into the seminal vesicles, particularly on the left side. The patient appeared acutely ill, had a high fever, and his urine contained many white cells and gave a heavy growth of E. Coli on culture. Acid phosphatase determination was 4.0 units. There was no evidence of metastases by Roentgen ray. Bilateral orchidectomy was performed and within 96 hours the clinical signs and symptoms produced by the blocked kidney disappeared and the urine became clear. Subsequent to this the patient has gained 20 pounds, is able to do light work around his farm and has remained well for 2 years. Shortly after orchidectomy several examinations showed that the prostate was definitely smaller in size, particularly in the region of the seminal vesicle on the left.

That the number of cases showing a decrease in size of the prostate and improvement of urinary function is small is not surprising when one considers that in many cases obstruction to urination is contributed to or wholly caused by benign prostatic hypertrophy, which so often occurs together with carcinoma of the prostate. One could, therefore, expect improvement of urinary symptoms only in those patients in whom the obstruction at the bladder outlet was largely due to malignant growth. It is our feeling that if urinary symptoms are severe enough to suggest the need for operative interference, this should be performed at the same time as orchidectomy rather than to wait for possible improvement from the latter procedure alone.

5. It has been repeatedly observed that the elevated serum acid phosphatase of patients with metastatic carcinoma of the prostate decreases following androgen depression therapy. The decline is most rapid during the first week after orchid-

ectomy, and thereafter a more gradual decrease occurs for the next 2 to 3 months. Of the 35 cases studied, 12 showed no clinical or Roentgen ray evidence of metastases and had a normal acid phosphatase. that is, 4 units* or less. Of the remaining 23 with metastases, 21 had acid phosphatase values above 4 units. All 21 cases displayed a reduction in acid phosphatase level after surgical castration, 12 of them ultimately returning to normal. In our experience this is of no prognostic significance, since a number of the patients whose acid phosphatase became normal and remained within normal limits succumbed within 3 to 10 months. On the other hand, in some cases a re-elevation of the acid phosphatase coincided with a clinical relapse and progression of metastatic involvement. The finding of a normal acid phosphatase in 2 of the cases with definite evidence of metastases by Roentgen ray is in keeping with the general experience of others. However, the serum acid phosphatase determination must be regarded as a valuable diagnostic aid, since a definitely elevated acid phosphatase (above 10 units) is almost never present in the absence of metastases.[9]

Discussion. Although the series reported is small, it is our feeling that the cases are varied enough to represent an adequate cross-section of the disease, its manifestations, and the results one may expect from orchidectomy as a method of treatment. Undeniably orchidectomy will prolong the life and comfort of a significant number of patients with metastases. In patients with advanced metastatic disease suffering severe pain and incapacitation, orchidectomy may result in dramatic improvement.

Unfortunately, there are few if any clinical or laboratory clues which enable one to foretell how any one patient will respond to surgical castration. However, the high percentage of immediately favorable results following this form of treatment makes its employment worthwhile in almost all cases.

The length of time during which a patient may be benefited by castration and remain free of pain varies considerably. The shortest period of improvement among our cases was 3 months, while the longest period of improvement to be followed by relapse lasted 24 months. As a rule the reappearance of pain was coincidental with rapid deterioration of the patient's general condition and was soon followed by death. In several such cases even large doses of stilbesterol failed to modify the downhill course of the patient or affect the pain.[2]

The question of the optimal time for orchidectomy has remained unanswered. Many authors advise withholding orchidectomy until metastases or symptoms thereof appear. Nesbit and Cummings,[7] for instance, express the opinion that, ". . . the maximum benefit to the patient may be derived by delaying endocrine treatment until indicated by the onset of symptoms arising from advanced or metastatic lesions." Others believe that the general life expectancy may be prolonged if orchidectomy is performed early, regardless of the presence or absence of metastases. Higgins (as quoted by Meads[6]) and others hold to this view. The possible beneficial effect of the operation on the local lesion as well as the possibility of delaying the appearance of metastases favor this opinion. It has been our policy in most cases to perform orchidectomy whenever the diagnosis of carcinoma of the prostate is made, regardless of the presence or absence of metastases.

Summary. Thirty-five cases of carcinoma of the prostate treated by orchidectomy have been studied.

Of the 23 cases with metastases, 12 died within 28 months and 11 are living, the

* One unit is defined as the degree of phosphatase activity which at pH 4.9 and 37° C liberates from a specified citrate buffer monophenylphosphate substrate solution 1 mg. of phenol in 1 hour, by the Gutman modification of the King Armstrong method for "alkaline" phosphatase. The number of units is determined to express the amount of phosphatase activity in 100 cc of blood serum (9).

longest for 25 months after operation. Of 11 cases without metastases, 5 are living, the longest for 30 months after operation.

Marked relief was experienced by one-half of the patients with pain within 48 hours, and slight to moderate relief occurred in the others. Improvement in well-being and appetite paralleled relief of pain in almost all instances.

Following orchidectomy the bony metastases showed increased density and became more discrete in the majority of instances, and sometimes also increased in size and number.

A decrease in size and softening of the original lesion was observed in a number of cases after operation, but improvement in urinary function attributable to orchidectomy alone occurred in only a few cases, and it was necessary to perform other operations to free the bladder outlet in 22 patients.

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THE FEMORAL BONE MARROW CELLS OF THE ALBINO RAT

By Mildred Vogel, M.D.*

(Department of Medicine, New York Medical College, Metropolitan Hospital Research Unit, New York City, N. Y.)

Numerous careful morphological studies of the peripheral blood of the albino rat have been published. The data have been well summarized recently by Griffith and Farris.[1] The same authors have referred briefly to the bone marrow, which they have regarded as similar to that of man save for its "preponderantly erythroblastic, pronormoblastic and normoblastic" character. Only two previously reported detailed studies of the bone marrow in the normal rat have been found, (Stasney and Higgins,[6] Toppner[7]). Additional information from a small group of control animals has been included in the reports of experiments on the effects of sulfanilamide (Higgins and Machella[2]).

Several difficulties are to be encountered in discussing the myelogram of man or of laboratory animals: (1) The variety of methods used by different investigators, (2) lack of uniformity in nomenclature and (3) failure to record the findings in a sharply defined manner. The present study is concerned with the development of a dependable method for obtaining data, the accurate description of cell types observed and a tabulation and classification of these.

Method. Twelve normal albino rats, of the Rockland strain, ranging in age from 6 to 8 months, were kept in the laboratory, from the time of birth, at a uniform temperature. They were fed exclusively on Rockland Farm Vitamin-D-free rat pellets (the standard diet used in our laboratory) and had free access to fresh water.

For obtaining each sample of bone marrow the animal was lightly anesthetized with ether. A dorsal incision was made parallel to the femur, the muscles were separated to expose the entire length of the bone, which was rapidly disarticulated and removed. During this procedure the amount of anesthesia was increased so that the animal expired at, or shortly after, the time the femur was completely removed. The bone was immediately bisected with a jeweller's saw and all of the marrow was withdrawn by a syringe through a 20-gauge needle and transferred to the center of each of a series of drops of saline, on separate slides, with which it was thoroughly mixed by rotating the tip of the needle. The smear was made in the usual manner by drawing the drop across the slide with a second slide. Simultaneously smears of peripheral blood were obtained by snipping the tail. The slides were air-dried for 30 to 60 minutes and treated, in the majority of instances, with Jenner-Giemsa stain. Wright's stain was used for at least one smear taken on each animal, and several of the total number of smears were stained with the Sato Peroxidase technique in order to identify cells of the myeloid series about which some doubt could be entertained. The differential count, in each instance, was based on the study of 1000 cells.

Results. I. Cell Types. Several types of cells were differentiated and classified. A description of each follows:

The "blast" cell is peroxidase-negative. It is round or slightly ovoid in shape and approximately 15–26 microns in diameter. It has a moderately dark, clear, blue cytoplasm. The nucleus is round and takes a light violet-colored stain. The darker-staining chromatin appears to form an over-all, fine, lacy or net-like structure. One to 5 small, well-defined nucleoli are invariably present: They take a lighter and bluer stain than the nuclear groundwork.

The promyelocyte is similar in size, shape and staining reactions to the "blast" cell. The nuclear chromatin, however, is ar-

* Emmanuel Maynz Fellow in Research, New York Medical College, Metropolitan Hospital Research Unit, New York City, N. Y.

ranged in heavier strands, forming a mesh-like pattern. Nucleoli, similar in number and staining reactions to those in the latter cell, are present although they frequently are less clearly defined. A few dark purple or azurophilic granules are noted in the cytoplasm. They are usually separated from the nucleus by a distance of 2 to 4 microns.

The myelocyte is round or ovoid in shape. It has a diameter of 14 to 20 microns. The violet-staining nucleus may be round or oval. The chromatin is arranged in fairly large, shallow heaps, giving the nucleus an unevenly furrowed or shaded appearance. Nucleoli are absent. The cytoplasm contains a varying number of granules. These may be small and lavender, or large and reddish-orange in color. Occasionally azurophilic granules, reminiscent of previous development stages, are observed. The cytoplasm, as seen between the granules, assumes a grayish-blue or pinkish-lavender cast. The cells are recognized, on the basis of the size and color of the granules, as the progenitors of the neutrophilic and eosinophilic granulocytes.

The "ring" cell is similar in size and shape to the myelocyte. The nucleus is round or ovoid and stains a violet color. The chromatin is arranged in moderately heavy clumps and coarse strands. Located at or near the central part of the nucleus is a well-defined ring-shaped opening, giving the nucleus a "dough-nut" appearance. With both the Jenner-Giemsa and Wright stains this opening has either a lilac or pinkish-yellow color. Lavender granules and, occasionally, small azurophilic granules are present in the cytoplasm, which assumes a moderately light blue or grayish-blue cast.

The metamyelocyte is round or ovoid in shape and has a diameter of approximately 12 to 16 microns. The cytoplasm takes a light grayish-blue, lilac or pinkish-yellow stain, the blue cast tending to predominate. It contains numerous distinct, small lavender granules or large, reddish-orange granules (neutrophilic and eosinophilic series, respectively). The nucleus, which is indented or kidney-shaped, is deep violet in color, with the chromatin concentrated in small, dense heaps and coarse interlacing strands. It is noted that the nucleus of the eosinophilic metamyelocyte takes a somewhat lighter stain than that of the neutrophilic metamyelocyte.

The staff cell (juvenile granulocyte, stab cell, rhabdocyte) is spherical in shape and approximately 10 to 16 microns in diameter. The cytoplasm is pinkish-yellow although the presence of lavender granules in the cells of the neutrophilic series tends to give it a lavender cast while the presence of orange granules in the cells of the eosinophilic tends to give the cytoplasm an orange-yellow cast. The nucleus of the cells of the former series stains a deeper violet than that of the cells of the latter series. The nucleus of the staff cell may be rod-shaped, curved in the form of a horseshoe or ring-shaped. There is no evidence of lobulation. The chromatin is arranged in coarse, interlacing strands.

The mature granulocyte is essentially like the staff cell in size, shape and cytoplasmic and nuclear staining reactions. The nucleus is lobulated. The lobulations, which are joined by fine, hair-like strands, range from 2 to 6 in number in the neutrophiles and from 2 to 3 in the eosinophiles.

The mature *basophilic granulocyte* is similar in size and shape to the other mature granulocytes. It has a light blue cytoplasm and an irregularly shaped, pale violet nucleus, which occasionally has a somewhat lobulated appearance. The presence of large, deep-staining purple granules in the cytoplasm tends to obscure nuclear detail and outline.

The erythroblast is round or ovoid in shape and varies from 8 to 20 microns in diameter. The cytoplasm, compared with that of the cells of the myeloid series, has a definitely opaque, rather than a translucent, clear quality. It may vary in the intensity of basophilic staining from a moderately dark to a very deep blue or greenish-blue, or it may exhibit numerous

degrees of polychromatophilia. Hemoglobin may be present as is indicated by the occasional occurrence of orthochromicity. The nucleus usually occupies one-half to two-thirds the diameter of the cell. It is round in shape and stains an intense, dark, purplish blue. Numerous block-like masses of basichromatin appear sharply demarcated from surrounding areas of paler-staining oxychromatin. In the majority of polychromatic erythroblasts the arrangement of the chromatin tends to give the nucleus a cartwheel appearance. Occasionally the nucleus is lobulated or star-shaped, in which instances very little oxychromatin is discernible. The cell is frequently seen in the process of mitosis.

The normoblast is spherical and has a diameter of approximately 7 to 10 microns. The cytoplasm is orthochromatic or polychromatic, rarely basophilic. The nucleus is round and has the appearance of a homogeneous, blue-black mass. It varies considerably in size in relation to the total cell, frequently occupying so much of the cell volume that only a narrow rim of cytoplasm is visible. Normoblasts containing pyknotic nuclei are occasionally noted.

The lymphocyte is round or ovoid in shape, approximately 7 to 14 microns in diameter, and has a clear, very light blue cytoplasm which may contain a few, fine, scattered red granules. The nucleus occupies an eccentric position and varies in size, occupying one-quarter to three-quarters of the total cell volume. It may be round or slightly indented in shape and stains a violet color. The chromatin structure is relatively coarse, basichromatin occurring in clumps which merge gradually into lighter-staining areas of oxychromatin.

The monocyte is similar in size and shape to the larger lymphocyte. The cytoplasm takes a grayish-blue stain and contains very fine, scattered, reddish-purple granules, which give it a "dusty" appearance. The nucleus may take the shape of a thickened horseshoe or appear folded back upon itself It stains a bluish-violet color, somewhat lighter than that of the lymphocyte. The arrangement of the chromatin resembles that of the latter cell.

The megakaryocyte is a large, irregularly shaped cell, amoeboid in type. It varies from 25 to 40 microns in its widest diameter. The cytoplasm stains a pale lilac color which tends to fade toward the periphery; it contains minute azurophilic granules which may be densely aggregated in some areas. The nucleus is large and irregularly shaped or lobulated. Chromatin, staining a dark, bluish-violet, is concentrated so as to outline lobular borders; the balance of the chromatin is arranged in small clumps enmeshed in fine filaments.

The macrophage, or *reticulo-endothelial* cell is ovoid in shape and approximately 15 to 30 microns in diameter. The cytoplasm takes a moderately deep blue stain. The nucleus may be round or lobulated and stains a dark blue: it is not too well delineated for the entire cell tends to have a cloudy appearance. Frequently engulfed erythrocytes or leucocytes may be observed within the cell membrane.

The "kugelhaufen" is irregular in shape and varies in diameter from 15 to 24 microns. A minute amount of lavender-staining cytoplasm may be seen: this is obscured, to a great extent, by the presence of relatively large purplish-black particles, resembling bullets or pieces of coal. These particles tend to break through the cell membrane and scatter in the immediate vicinity of the cell. An eccentrically placed round or ovoid, pale lavender-staining nucleus is noted: this is traversed by numerous fine interlacing strands of violet-colored chromatin.

The plasma cell is ovoid in shape and approximately the size of the larger lymphocyte. The cytoplasm appears dense and opaque and takes a deeply basophilic stain except in the perinuclear area, which is relatively pale. Occasionally small vacuolated areas, resembling bubbles, are noted in the cytoplasm. The nucleus, which is round, is approximately one-third to one-half of the diameter of the cell:

it almost invariably occupies an eccentric position. Basichromatin, staining a very deep blue or bluish-purple color, is divided into relatively large blocks, sharply demarcated from the sparser oxychromatin, and is arranged in a cartwheel, or radiating manner.

as above described. In each instance, not less than 1000 cells were differentiated in a single specimen. The results are tabulated in Table 1.

Similar data for the peripheral blood of the rats studies are included in Table 2.

Each element of the blood of the rat

TABLE 1.—DIFFERENTIAL COUNT OF THE CELLS FOUND IN THE BONE MARROW OF TWELVE NORMAL ALBINO RATS (1000 CELLS)

Myeloid/Erythroid ratio—1.78 (average).

Cell Type	No. of cells per 1000 cells Range	Mode	Mode—Number of rats In	Below	Above
Mature neutrophiles	168–281	230–245	6	4	2
Neutrophilic staff cells	76–220	110–150	6	4	2
Neutrophilic metamyelocytes	24–48	30–42	8	1	3
"Ring" cells	42–90	49–65	8	2	2
Neutrophilic myelocytes	16–40	20–30	5	3	4
Bromyelocytes	3–18	6–12	8	2	2
Mature eosinophiles	25–70	40–47	8	2	3
Eosinophilic staff cells	12–60	24–42	7	3	2
Eosinophilic metamyelocytes	6–19	6–13	7	3	2
Eosinophilic myelocytes	1–5	2–3	6	2	4
Mature basophiles	0–2	1	4	6	2
"Blast" cells	23–61	29–43	5	2	5
Erythroblasts	80–160	100–120	8	2	2
Normoblasts	188–300	220–240	8	2	2
Lymphocytes	18–53	25–45	7	2	3
Monocytes	0–6	2–4	9	2	1
Plasma cells	4–10	4–6	7	0	5
Megakaryocytes	0–16	1–3	8	3	1
Macrophages	0–4	1	8	2	2
"Kugelhaufen"	0–2	1	5	4	1

TABLE 2.—DIFFERENTIAL COUNT (100 CELLS) OF THE PERIPHERAL BLOOD OF TWELVE NORMAL ALBINO RATS

	Neutrophiles	Lymphocytes	Monocytes	Eosinophiles
Range (per cent)	16–38	53–81	0–3	1–12
Mode (per cent)	22–30	64–77	1	2–6
Rats in (No.)	6	7	2	6
Rats below (No.)	3	2	9	4
Rats above (No.)	3	3	1	2

The degenerated cell (basket cell, smudge cell) is one which has either degenerated due to senility or which, because of its fragility, has been broken in making the smear. It is irregular in outline, takes a uniform reddish-violet or bluish stain and shows a loss of nuclear and cytoplasmic structure. A small percentage of cells of this type are present in all smears. They cannot be identified with any certainty.

II. THE PERCENTAGE OF THE VARIOUS TYPES OF CELLS ENCOUNTERED IN THE FEMORAL BONE MARROW AND PERIPHERAL BLOOD OF THE RAT, RESPECTIVELY. Counts of the femoral bone marrow were made from diluted smears fixed and stained

showed a greater normal variation than the same element in the blood of the healthy human being. It was therefore not surprising to find a broad range of values for the elements of the bone marrow in normal rats. Because of this, attempts to express the results in averages, or as means, with standard deviations, seemed to have little value. Tables were constructed to show the range, the mode, and the number of rats falling in the mode and below and above it.

Discussion. The study of hemopoiesis in pre- and post-natal life has given rise to several theories regarding the origin of blood cells. The polyphyletic, or trial-

istic, theory briefly states that the reticulo-endothelial cell gives rise to an extravascular, or "free cell" which is present in all leucopoietic tissue: this in turn gives rise to the myeloblast, lymphoblast and monoblast. The endothelial cell lining the vascular system of the bone marrow gives rise to megaloblasts which are the progenitors of the cells of the erythroid series.

The megaloblast has been described as a large cell, with an opaque, densely-staining cytoplasm and a coarse arrangement of the nuclear chromatin. Megaloblasts may be observed in adult human bone marrow under pathological conditions. Their presence in the bone marrow of normal adult albino rats has not been reported, nor were cells of this type noted in the smears of bone marrow studied in the present investigation. In the human the myeloblast, lymphoblast and monoblast have been described as peroxidase-negative cells, with similar cytoplasmic and nuclear morphology and staining reactions, properties which render differentiation uncertain and difficult. These cells have been grouped together here under the heading of "blast" cells. It is believed that myeloblasts are preponderant, because (1) of the relatively small total number of lymphocytes and monocytes present in the marrow and (2) microscopic examination of histological sections of the femur of the rat showed only a very occasional lymphoid follicle.

The promyelocyte differs morphologically but slightly from the "blast" cell. That it is a precursor of the granulocyte is evident because of the presence of a few scattered granules in the cytoplasm. In this stage of development it is impossible to designate the cell as the precursor of a specific type of granulocyte. Töppner[7] classifies the "ring" cell as a promyelocyte: this point is discussed below.

The myelocyte and metamyelocyte as here classified do not differ from those described by other authors.

The "ring" cell is believed to occupy an intermediate position between the myelocyte and the metamyelocyte for the following reasons: (1) The opening, or "ring," in the nucleus is thought to represent a primary step in the formation of the typical indented nucleus of the metamyelocyte, (2) the staining reaction of the cytoplasm within the "ring" is frequently acidophilic, resembling that of the more mature cell, and (3) the presence of numerous granules favors an advanced position in the line of descent. It is noted, however, that no eosinophilic granules were observed in "ring" cells.

The staff cell might be classified in two separate groups on the basis of nuclear morphology. It is believed that the more immature form has the horseshoe-shaped, or elongated nucleus described by so many authors and that those cells in which the nucleus is non-lobulated and ring-shaped represent the stage in development closest to the mature cell.

The mature granulocyte described herein does not vary from that described by other authors. The presence of the basophilic granulocyte in this group is worthy of attention. No cells resembling progenitors of this type were observed. The basophile is infrequently noted in the bone marrow of the rat (Higgins and Machella[2]), other laboratory animals and the human (Plum[4]) (Table 1). In approximately 700 differential counts (100 cells) of the peripheral blood of rats, made in this laboratory in connection with this and other experimental procedures, only *one* basophile was observed.

The cells of the erythroid series have been divided into two groups for purposes of simplification. The term erythroblast is used to include the cells designated by others under the various headings of pro-erythroblasts, erythroblasts, macroblasts, pronormoblasts, etc. It is felt that to subdivide these cells on the basis of differences in size and cytoplasmic staining reaction, which does not appear to have a direct relation to size, is unnecessary and confusing. Contrasted with the normoblast the erythroblast is larger and its nucleus exhibits a definite pattern of the

chromatin. The cytoplasm of cells of both types may take similar stains, although hemoglobin tends to be present in greater amounts in the more mature elements. A high percentage of erythroblasts exhibit a dark grayish-lavender or deeply basophilic cytoplasm: these are believed to represent the more embryonic forms. It is of interest that the mature erythrocyte, both in the bone marrow and the peripheral blood of the rat exhibits a marked degree of polychromatophilia.

The lymphocyte, monocyte and plasma cell are identified here in a manner similar to that used by other workers. The polymorphonuclear leucocyte-lymphocyte ratio in the peripheral blood of rats is the reverse of that in human beings (Table 2). The percentage of lymphocytes present in the bone marrow of rats is, however, somewhat lower than that reported for man. The percentage of monocytes in the peripheral blood of rats, as in the human being is relatively much greater than that in the bone marrow. The percentage of plasma cells in the bone marrow of the rat and in that of the human being are similar.

The megakaryocytes of the rat and of the human do not differ.

According to Toppner[7] the "kugelhaufen" has been described by Landa and Flaun and Kleineberger. They have been classified as reticulo-endothelial in origin. The "bullets", or particles of intensely dark-staining material, are of unknown origin. These cells resemble those described by Maximow and Bloom[3] as macrophages (histiocytes, clasmatocytes, wandering cells) and the particles are thought to be ingested blood pigments. Smaller but similar cells are the wandering cells of the tissues, such as the "dust cells" in the lung, encountered in the human, and the "mast" cells, seen in areas of inflammatory reaction in the rat.

One of the greatest disadvantages encountered in obtaining a sample of bone marrow was the necessity for sacrificing the animal. The possibility of carrying out successive studies was thereby eliminated. The femoral medulla has a diameter of 1.5 to 3 mm. The bony cortex, although less than 1 mm. in thickness, is extremely hard and attempts to enter the exposed shaft in the living animal, with the needles available, were unsuccessful.

The method used eliminated contamination of the marrow by peripheral blood. The bone marrow of the rat is extremely hyperplastic: It presents a pink to reddish-gray appearance and is moderately thick in consistency. Attempts were made to count cells in undiluted marrow in accordance with the methods of Töppner[7] and Stasney and Higgins.[6] These counts were not accurate because of the thickness of the smears and the resulting overlapping of a high percentage of the cells. The difficulty of making a correct differentiation of cell types under such conditions is obvious. It is further believed that the counting of consecutive cells, rather than the counting of cells in selected fields, yields a more accurate estimation of the percentage of cell types present.

Counts of the various types of cells were also made on sections of femur, fixed in Zenker's solution and stained with Wohlbach's modification of the Giemsa stain. The shrinkage of cells during fixation rendered identification difficult.

The differential counts made on peripheral blood of the 12 rats fell within the normal limits of many counts not only as made in this laboratory but also as reported by others (Griffith and Farris[1]; Scarborough[5]).

Summary. A new technique for obtaining smears of femoral bone marrow of the rat is detailed.

The types of cells observed in the femoral bone marrow are described and their interrelationships discussed.

On the basis of morphologic studies of the femoral bone marrow in 12 adult albino rats tables have been constructed to show the distribution by percentage of the various cellular elements; the range and modal values for each have been determined.

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POSTPARTUM BLOOD: ITS CLOTTING MECHANISM AND RELATIONSHIP TO THE PERIPHERAL BLOOD PICTURE

By Allan C. Barnes, M.S., M.D.
ASSOCIATE PROFESSOR OF OBSTETRICS AND GYNECOLOGY, THE OHIO STATE UNIVERSITY MEDICAL SCHOOL

That menstrual blood is a unique non-clotting fraction has been long known, and its "coagulation defect" has been repeatedly studied.[2,6,8,9] The non-clotting nature of postpartum blood has also been observed,[7] but we know of no studies as to the etiology of this phenomenon. Because of the potential value of such information in the management of the pregnant patient with hemorrhagic disease and in the problem of postpartum hemorrhage, the clotting mechanism of postpartum blood, its nature and its relationship to the clotting mechanism of the circulating blood have been studied.

Postpartum blood was collected by 2 methods: (*a*) 1 hour after delivery a vaginal diaphragm was put in place which was removed from 2 to 12 hours later and the contained specimen studied, or (*b*) a sterile 50 cc. test tube was held in the vagina above the level of the episiotomy wound and the fundus gently massaged as the specimen was collected directly. All peripheral blood samples used for comparative studies (defibrinated, heparinized, clotted, etc.) were human blood. Since it was immediately determined that postpartum vaginal blood has both the blood type and Rh classification of the circulating blood, in all procedures which involved mixing peripheral and postpartum blood (clot lysis, seeding, etc.) both samples were taken from the same patient. The thromboplastin employed was the standard material used for prothrombin determinations (Difco). The crude human fibrinogen (Lilly) and the thrombin (Parke-Davis) were issued for investigational use. Clotting times were determined at room temperature by the method of Lee and White.[12]

Procedures and Results. No. 1. Postpartum blood does not clot spontaneously and will not clot when any of the following elements are added singly: calcium, trypsin, fibrinogen, thromboplastin, thrombin. The single absence of any of these substances, or the presence of a specific inactivator against one of these is therefore ruled out. This also eliminates an analogy with oxalated and citrated blood, which clot on the addition of calcium; as well as with heparinized blood and recalcified plasma, both of which clot on the addition of thrombin. For control purposes in the further studies, accordingly, these incoagulable forms were not used. Control experiments were run with defibrinated blood, prepared by the glass bead method and "serum plus cells." This latter fraction was made by resuspending the patient's saline-washed cells in her own serum in a concentration adjusted to approximately 50% of the original red cell count.

No. 2. 0.1 cc. of postpartum blood and of the control bloods were placed in test tubes and 2 cc. of freshly drawn venous blood was added to each. The clotting times so obtained were repeatedly consistent, the results in a single typical experiment being shown in Table 1. It can be seen that there is no evidence of an anticoagulant in any of these bloods, but rather a clot-promoting activity. Such clot-promoting action on normal blood is not possessed by citrated blood.[9]

Table 1.—Clotting Times of Venous Blood (2 cc.) With Addition of Blood Fractions Under Examination (1 cc.)

Substance added	Minutes
Nothing (Control)	6
Oxalated plasma	6½
Defibrinated blood	3
Cells plus serum	2½
Postpartum blood	3

No. 3. While the failure to clot on the addition of thrombin would point to a

deficiency in fibrinogen, the single addition of fibrinogen, as indicated above, failed to produce clotting. Two mixtures were prepared, therefore, 1 of thromboplastin and thrombin, the other of thromboplastin and fibrinogen. One cc. of each mixture (*i. e.*, an excess) was added separately to 1 cc. samples of the bloods under study. The results of a typical experiment are shown in Table 2. In its reaction to thromboplastin, fibrinogen and thrombin, therefore, postpartum blood behaves like defibrinated blood or a suspension of cells in serum.

TABLE 2.—CLOT FORMATION ON ADDITION OF THROMBOPLASTIN AND THROMBIN (NO. 1) AND OF THROMBOPLASTIN AND FIBRINOGEN (NO. 2) IN EXCESS

Blood studied	Mixture No. 1	Mixture No. 2
Defibrinated	No clot	Clot
Serum plus cells	No clot	Clot
Postpartum blood	No clot	Clot

No. 4. When postpartum blood is "seeded" with small amounts of fresh unclotted venous blood, clotting occurs.[7] By repeated determinations with serial amounts of venous blood added, it was found that the minimal amount which would produce this phenomenon was about 2 drops per cc. of vaginal blood. It was also determined that the addition of this same amount of oxalated blood, serum or plasma was ineffective in producing clotting. Defibrinated blood and serum plus cells show the same "seeding" reaction and will clot when 2 drops per cc. of freshly drawn venous blood are added. This phenomenon may well account for the postpartum clots occasionally passed (*i. e.*, the seeding from small cervical tears).

No. 5. The proteolytic action of menstrual blood has been reported.[8] A possible proteolytic activity in postpartum blood was investigated as follows: samples of 1 cc. of postpartum blood were incubated at 37° for 48 hours against each of the following: 2 cc. clotted blood (drained of its serum), crude human fibrin, washed from the beads following the defibrination of 30 cc. of blood, and 2 cc. of serum clotted by the addition of minute amounts of fibrinogen. In each case the substrate was weighed before and after incubation, and the digestion expressed as % of weight lost. Since these figures are determined from wet weights, they are subject to error and must be interpreted liberally. The average of 5 determinations in each case was taken, and are shown in Table 3. It can be seen that postpartum blood displays no tendency to lyse crude fibrin, and that its lytic action against clotted serum and whole blood clot, while definite, is not marked. A more pronounced lytic action has been reported for other body fluids and extracts.[8]

TABLE 3.—THE PERCENTAGE OF WEIGHT LOSS OF CLOT FRACTIONS WHEN INCUBATED 48 HOURS WITH POSTPARTUM BLOOD

Substrate	Weight loss	
	Control (%)	Digested (%)
Fibrin	8	16
Clotted serum	10	45
Whole clot	15	50

COMMENT. The data developed from the above experiments indicate that the blood discharged from the uterus in the postpartum period behaves in its clotting reactions like defibrinated blood. It has a weak proteolytic action, and a clot-promoting activity. Since its behavior is essentially that of a suspension of cells in serum, 2 questions immediately arise: (*a*) Is the cell content constant, or does it fluctuate, and what is its relation to the cellular elements in the circulating blood? (*b*) Is its chemistry that of the patient's serum?

No. 6. Complete cell counts and differential determinations on the peripheral and uterine bloods were made daily on 10 patients for a period of 5 days postpartum. The results are indicated in Figure 1. It can be seen that the red cell content and hemoglobin never equal those of the circulating blood, and diminish daily. Due to persistent clumping, which was overcome with difficulty, the white cell count is less accurate, but it starts at a low level and rises rapidly, exceeding

the peripheral count in all cases within 36 hours of delivery. Although the lymphocyte count of the vaginal blood tended consistently to be lower, the difference was not great, and the differential count of the vaginal blood in general roughly reflected that of the peripheral blood. The platelet count was in all cases low (average 36,000 per c.mm.).

No. 7. Routine chemical studies were carried out on specimens of vaginal blood collected the 1st day, controlled by similar determinations on the patient's circulating blood. Blood chloride and cholesterol

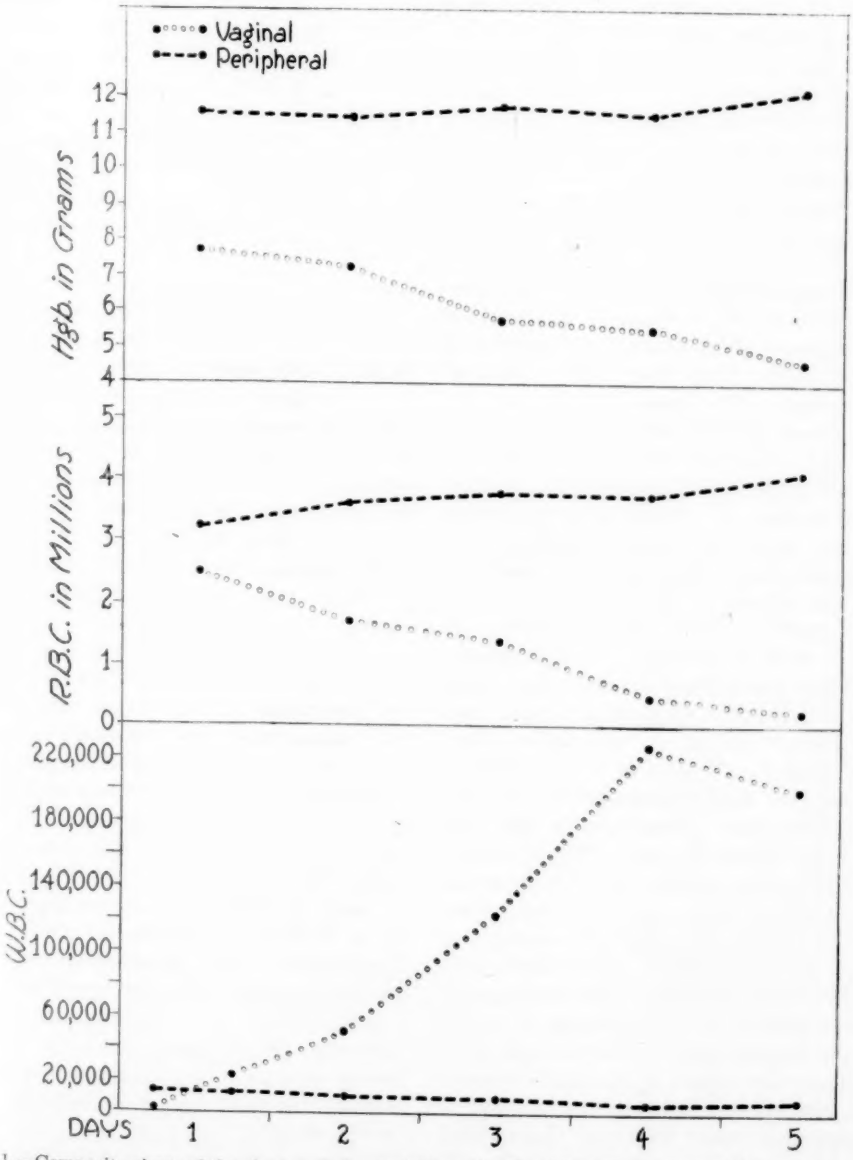


FIG. 1.—Composite chart of the changes in hemoglobin, red cell, white cell elements of the postpartum blood during the first 5 days of the puerperium.

levels were normal, as was the sedimentation rate. We did not discover in postpartum blood the elevated nitrogen levels reported for menstrual blood,[11] and the NPN and BUN on 7 samples of blood consistently ranged on the low side of normal, with the exception of a single BUN determination of 32 mg. It should be noted that all of the above results (whole blood determinations) were within normal range, but that in all (except the single BUN cited), the levels discovered in the vaginal blood were lower than those in the venous blood. These results conform with the hypothesis that vaginal blood is serum containing cells and cellular débris but with a lower count than the peripheral blood.

Serum calcium levels closely approximated those of the circulating blood, and the sugar levels were normal on specimens collected by test tube and examined promptly. The total proteins of the vaginal blood were reduced slightly (average 5.7), the loss being in the albumin fraction (average 3), with the A/G ratio approaching 1. This, however, agreed roughly with the control (venous) blood determinations which similarly showed a lowered albumin level (average 3.15).

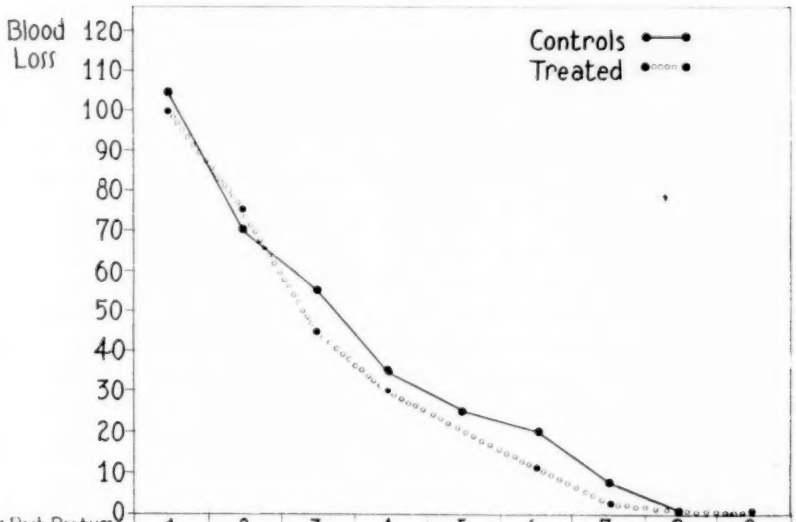
Comment. Postpartum "blood" appears to be a serum-plus-cells suspension in which the cellular elements vary daily, but with a fairly constant pattern in their variation. It has no coagulation time, and since it will not clot on the addition of calcium and thromboplastin, no prothrombin time. Teleologically speaking, it is not meant to clot. The process of clot formation within the uterine cavity has nothing to do with the blood coming from the postpartum uterus. A question immediately arises which is of interest and importance both in the problem of postpartum hemorrhage as well as in the management of the puerperium in patients with blood dyscrasias: What is the relationship between the amount of postpartum blood lost and the clotting mechanism of the peripheral blood?

No. 8. By means of dicoumarol and heparin administered in the early puerperium, the prothrombin time and the coagulation time were prolonged while the amount of vaginal blood lost was measured. The method of measuring vaginal blood loss and the experimental details have been described in the portion of this work reported.[1] The results of 10 control patients contrasted with 20 patients receiving dicoumarol are shown in Figure 2. It can be seen that the blood loss for the group with depressed prothrombin levels (Quick method) did not differ essentially from the blood loss of the control group.

Figure 3 indicates the results obtained when the clotting time was prolonged with heparin in 6 patients during the 1st postpartum day. Again it can be seen that there was no increase in the amount of uterine bleeding. Similarly, a group of patients were given vitamin K during labor to determine if there was any diminution in blood loss. One ampule of hykinone administered during labor, however, failed to raise the already elevated prothrombin level, and the blood loss suffered by this group (6 patients) was exactly that of the control group.

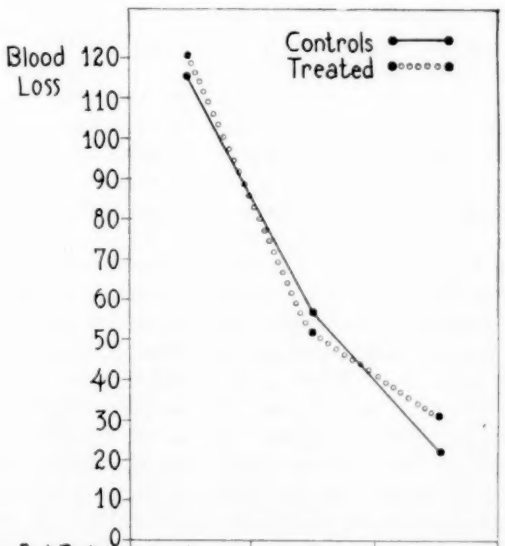
Discussion. It can be concluded from the above that there is a complete divorce between the prothrombin and coagulation times of the circulating blood, and the amount of blood lost from the uterus in the puerperium. While such conclusions have considerable importance in the management of the patient with hemorrhagic tendencies, it must be stressed that they apply only to blood coming from the uterus. A cervical laceration or an episiotomy in such a patient could be expected to bleed as freely as would a laceration or an incision elsewhere on the body. Furthermore, these experiments warrant conclusions only with reference to uterine bleeding after the placenta has been delivered. Blood coming from the uterus during pregnancy or labor is a normally clotting fraction similar in behavior to venous blood.

Changes in the clotting and prothrombin mechanism alone do not reproduce the



		Days Post Partum	1	2	3	4	5	6	7	8	9
Average Prothrombin Levels	Controls		114%	110	112.5	112.5	100	109	108	101	96
	Treated		90.2%	52	33	36	20	42	36	54	66

FIG. 2.—Blood loss measurements reported in terms of an arbitrary scale for a group of control patients in the first 9 postpartum days contrasted with a group of patients who received dicoumarol to depress the prothrombin levels.



		Days Post Partum	1	2	3
Average Coagulation Time (Min)	Controls		6	6	7
	Treated		Held at 18-25 for 10 hr period	6½	6½

FIG. 3.—Blood loss during first 3 postpartum days of a group of control patients contrasted with a group receiving sufficient heparin the 1st day to elevate the clotting time for a 10 hour period.

picture in the thrombocytopenias. The platelet count cannot be so conveniently and temporarily altered on an experimental basis, but during the course of this study an opportunity presented itself to deliver a patient with monocytic leukmia. Her platelet count at the time of delivery was 68,000 and she had been displaying generalized hemorrhagic tendencies during the 6 days prior to the onset of labor. Immediately following delivery she was put on the same oxytoxic schedule as the group of control patients cited in Figures 2 and 3 (ergotrate, $\frac{1}{3}\frac{1}{2}\frac{}{0}$ gr., intravenously, following the delivery of the placenta, and by mouth 3 times a day the 1st and 2nd postpartum days). Her blood loss during the first 24 hours postpartum was about two-thirds that of the controls, and by the 2nd day had fallen to a level which could not be measured with accuracy. Bright and Hayes[3] have noted in a recent report of a patient with acute lymphatic leukemia in pregnancy that "postpartum hemorrhage, contrary to expectation, was easily controlled." Such an "expectation" is based on the assumption that the clotting defect in the circulating blood will be reflected in the amount of postpartum bleeding. It is interesting to note, however, that in the 76 cases of leukemia in pregnancy collected by McGoldrick and Lapp[10] there is only 1 death from postpartum hemorrhage recorded (attributed to uterine atony). Another postpartum death occurred from bleeding, but the patient had been subjected to Cesarean section and the possibility of the bleeding being from the uterine and/or abdominal incisions is not ruled out. Finn[4] in his survey of the literature and report of cases of thrombocytopenic purpura in pregnancy states that "most authors agree that no hemorrhage occurs at the time of delivery." From our own experience, therefore, as well as from the reports in the literature, the influence of a diminished platelet count on postpartum bleeding is apparently not the same as is its reported effect on menstruation.[5]

Abnormal bleeding states are usually associated with one or more of the following: (1) alterations in the clotting mechanism; (2) qualitative or quantitative changes in the platelets; and (3) increased permeability in the capillary wall.[13] On the basis of experimental alterations in coagulation and prothrombin times reported here, and of observed and reported cases with lowered platelet counts, it is apparently possible to draw the conclusion that there is little, if any, relationship between the first and second groups of changes and the tendency to bleed excessively during the postpartum period. The ability of the blood to clot, the normal body defense against blood loss, apparently plays little part in the problem of postpartum uterine hemorrhage. The relationship of capillary permeability remains to be investigated, but undoubtedly the most important single factor influencing the amount of blood lost following delivery is the mechanical closing of the sinuses in the placental bed, which is dependent on the efficiency of the uterine contraction and unrelated to the coagulation tendencies in the circulating blood.

Conclusions. 1. The "coagulation defect" of postpartum uterine blood has been studied: (*a*) This blood fraction does not clot *in vitro* spontaneously or on the addition of any one of the following substances singly: calcium, thromboplastin, trypsin, fibrinogen or thrombin. Accordingly, it does not resemble oxalated, citrated or heparinized bloods, or recalcified plasma. (*b*) It displays a clot-promoting action and a definite but weak proteolytic activity. (*c*) Postpartum blood will clot on the addition in excess of a mixture of thromboplastin and fibrinogen, or on "seeding" with small amounts of freshly drawn venous blood. In these respects it behaves in a manner similar to defibrinated blood or a suspension of cells in serum.

2. Hematologic and chemical characteristics of postpartum uterine blood have been investigated: (*a*) Its cell count varies daily during the puerperium. (*b*) This variation follows a characteristic pattern,

with the hemoglobin and red cell count dropping steadily, while the white cell elements rise rapidly. (*c*) The blood chemical analyses give results which would be anticipated for a suspension of cells in serum.

3. The effect of variations in the clotting mechanism of the peripheral blood on the amount of postpartum blood lost has been measured: (*a*) Prolongation of the prothrombin and clotting times (by dicoumarol and heparin) did not increase the amount of postpartum blood lost. (*b*) The administration of vitamin K was without effect in raising the (already elevated) prothrombin level of the patient immediately postpartum, and was without effect in diminishing vaginal blood loss. (*c*) A patient with monocytic leukemia and a platelet count of 68,000 at delivery had a smaller postpartum blood loss than the control patients in this series. The literature reporting thrombocytopenic dyscrasias in pregnancy shows no correlation with hemorrhage. (*d*) Although it has been assumed to exist, no definite relationship can be established between the peripheral blood coagulability and the amount of postpartum bleeding.

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THE EFFECT OF CIRCULATORY FACTORS ON THE BROMSULPHALEIN TEST IN LIVER DISEASE

By Nathan Blumberg, M.D., F.A.C.P.
and
Eugene M. Schloss, M.D.

(From the Medical Service of the Senior Author, Jewish Hospital, Philadelphia, Pennsylvania.)

The bromsulphalein test, introduced by Rosenthal[7] in 1922 and elaborated by Rosenthal and White[8] in 1924, has had wide clinical trial over a period of many years. It has a prominent position among tests of liver function because of its ease of performance and specificity as a test for hepatic excretory capacity. However, it is inadequate in disclosing minor grades of hepatic dysfunction in local lesions which do not encroach upon the liver's reserve of original or regenerated tissue. But, once damage is sufficiently extensive to be demonstrated by the test, its value is enhanced by serial repetition to indicate quantitative fluctuations at appropriate intervals. The recent adaptation of the photoelectric method in the determination of bromsulphalein retention should further increase its usefulness by eliminating the difficulty in matching icteric sera.

A method which involves the introduction of a dyestuff into the circulating blood stream, its excretion almost exclusively by the hepatic cells, and the measurement of the dye remaining in the blood stream after a given time, involves but 2 factors: namely, the functional status of the liver with regard to dye excretion, and the functional integrity of the blood circulatory system. For many years, the intimate connection of circulatory insufficiency and hepatic dysfunction has been studied. Frequently the bromsulphalein test has been used together with the Van den Bergh reaction and others to assess hepatic insufficiency in cardiac failure. In 1930, Jolliffe[5] using a 2 mg. per kilo body weight dosage of the dye, concluded that impairment of liver function induced by chronic passive congestion apparently was not permanent, whereas that still in evidence after recovery from the congestion probably indicated an independent liver involvement. In 1932, Robertson, Swalm and Konzelman,[6] studying the comparative merits of 5 liver function tests in cardiac decompensation, concluded that the bromsulphalein test gave results of less significance than did the icterus index. However, their figures on bromsulphalein retention at 30 minutes, with the 5 mg. dose, would appear to substantiate a higher evaluation. In discussing hepatic function in portal cirrhosis and congestive heart failure, Cantarow[3] stated that hepatic functional impairment, as indicated by retention of bromsulphalein, is present in practically all cases of myocardial failure with hyperbilirubinemia. Boland and Willius,[2] concluded that in cases of congestive heart failure, minor grades of dye retention were disclosed frequently, whereas marked degrees of impairment of hepatic function were uncommon. However, it remained for Bernstein, LeWinn and Simkins[1] to attempt more precise methods of evaluation of the purely circulatory and purely hepatocellular components in the production of demonstrable bromsulphalein retention in heart disease. In 59 cases they reported the bromsulphalein (5 mg. dose) test, venous pressure readings, magnesium sulphate and ether circulation time determinations, and clinical evaluation of the patients. They found that the dye excretion was normal in the absence of heart failure, that mild degrees of heart failure appeared to present parallel impairment of the bromsulphalein and circulation time tests, that bromsulphalein retention was nearly always present in severe grades of heart failure. However, no mathematical

correlation was demonstrable. Chávez, Sepúlveda and Ortega,[4] utilizing several hepatic function studies in heart failure, concluded that blood bilirubin, bromsulphalein and urinary urobilinogen determinations were perceptibly parallel and usually correlated with the degree of heart failure. They did not attempt the differentiation of circulatory and hepatic factors suggested by Bernstein, *et al.*

With the foregoing observations of hepatic function in known cardiac disorders in mind, we investigated the status of the test in known cases of hepatobiliary disease in which cardiovascular disorders were coexistent to determine possible effects of impaired circulation. A group of 14 patients with hepatic disorders and clinically established cardiovascular abnormalities were followed over a period of time. The procedures used were the bromsulphalein test, venous pressure reading, and circulation time determination, performed in that order. In the bromsulphalein test the dose was 5 mg. per kilo and a single specimen was taken at exactly 30 minutes. The standard of normality was 10% or less retention. On withdrawing blood for the 30-minute specimen, an L-tube manometer was attached for direct measurement of the venous pressure in centimeters of blood. When that measurement was concluded, 2.5 cc. of 20% calcium gluconate was rapidly injected through the same 18-gauge needle, and the arm-to-tongue circulation time determined. Thus, the entire procedure could be accomplished with but 2 venipunctures. Venous pressure readings between 4 and 12 cm. were considered within normal limits and the normal range of circulation time was taken to be 9 to 16 seconds. In some instances, to reduce discomfort and anxiety to the patient, the venous pressure determination was omitted.

The diagnosis of liver disease in this group was established by standard clinical and laboratory observation, the latter including determinations of icterus index, Van den Bergh reaction, urobilinogen studies (Wallace and Diamond technique), galactose tolerance test, cholecystography and, in some instances, biliary drainage. The group included cases of acute infectious hepatitis, chronic hepatitis following that disease, metastatic carcinoma of the liver, and hepatic cirrhosis. In each instance, particularly in the cirrhotic patients, care was taken to exclude cases in which any direct relationship could be established between the cardiovascular and hepatic factors etiologically. Although none of these patients are known to have come to autopsy at this time, we believe that throughout the group these 2 entities have been relatively separate insofar as clinical observation, hepatic function tests, electrocardiography, radiologic cardiac measurement, venous pressure, and circulation time could tell. Results of the study are detailed in Chart 1.

Discussion. While no major generalizations can be drawn from this comparatively small series of cases, there would appear to be some justification for certain limited conclusions. It is obvious that in each case, the excretion of bromsulphalein has been infringed upon by the dual factors of hepatic disease and circulatory inefficiency. Just as in the cases described by Bernstein, *et al.*,[1] it is equally clear that no mathematical formula by which a percentage role could be assigned to the individual components is indicated by this study. Nevertheless, it is of interest to examine certain aspects of the results.

In the acute infectious hepatitis group, Cases 2 and 4 underwent some break in compensation for which we can offer no adequate explanation. In each instance, presumably, the patient was on bed rest and, as far as could be ascertained, there was no relapse of hepatitis demonstrable by fever, re-enlargement of the liver, palpation or rebound tenderness or alteration in icteric index. Unfortunately, neither methylene blue nor readily performed quantitative urinary urobilinogen techniques were available at the time. However, over and above the abnormal brom-

sulphalein readings made from 4 to 8 days prior to the break in compensation, there occurred a notably increased bromsulphalein retention associated with abnormality of the circulation time and venous pressure. Once compensation was restored and circulation time and venous pressure had returned to their normal or former levels bromsulphalein readings were found to have decreased even below their prior

CHART 1

Case	Age	Interval Between Tests	Clinical Data	Bromsulphthalein	Circ. Time	Ven. Pres.	Hep. Enl. (Cm.)
ACUTE INFECTIOUS HEPATITIS							
1.	29		Convalescent; old mitral stenosis, compensated	20	18	..	0
		14 d.	Mild relapse of hepatitis with break in compensation, basal rales	70	20	..	2
		29 d.	Convalescent; compensation restored	20	19	..	0
2.	26	.....	Convalescent; old mitral stenosis, compensated	20	16	..	1
		8 d.	Icterus index unchanged at 10 units but mild pulmonary congestion	45	23	16	3
		22 d.	Compensation restored; no hepatitic activity	10	17	10	0
3.	41	.....	Peak of mild hepatitis; old mitral stenosis, compensated	60	17	10	3
		14 d.	No change in cardiovascular status	20	19	10	0
		21 d.	Convalescence complete	10	19	10	0
4.	31	.....	Convalescent; aortic stenosis, compensated	20	18	12	1
		4 d.	Frequent ventricular extra-systoles and mild dyspnoea at rest; icterus index unchanged	35	22	17	2
		30 d.	Normal rhythm and compensation; icterus index unchanged	18	18	12	0
5.	26	.....	Convalescent; mitral stenosis, compensated; icterus index 8 units or less 15 days	10	11	9	0
		11 d.	4th day of exercise tolerance series; icterus index 9 units; moderate dyspnoea on walking	35	18	13	1
		10 d.	Complete rest during interim; no evidence of broken compensation after 3rd day; icterus index 9	10	12	8	0
CHRONIC HEPATITIS							
6.	27	.....	Mitral stenosis, compensated; apparently normal convalescence from acute infectious hepatitis. Icterus index 17 units 6 weeks after inception of jaundice	60	14	..	2
		1 mo.	Good compensation; icterus index 11	25	15	9	1
		2 mo.	Icterus index 14 units; continued fatiguability, hepatic rebound tenderness	25	15	8	2
		2 mo.	3rd day of exercise tolerance test with icterus index 17, serum proteins 6.0 gm., A/G ratio 2.4; mild dyspnoea at rest	55	20	12	4
		1 mo.	Complete bed rest since last observation; icterus index 14; rebound hepatic tenderness; anorexia	25	14	8	2
METASTATIC CARCINOMA OF LIVER							
7.	64	.....	Primary lesion: stomach. Generalized arteriosclerosis with radiological evidence all extremities. Icterus index 9, serum proteins 6.3 gm., A/G ratio 2.1.	10	13	..	1
		2 mo.	During 36-hour attack of mild dyspnoea, bilateral basal rales, mild dependent edema; serum protein 6.2 gm., icterus index 10, A/G ratio 2.3	25	19	16	3
		3 w.	Complete bed rest during interim; icterus index 10 units	14	12	9	1
8.	49	.....	Primary lesion: right breast. Primary pernicious anemia without anemia; generalized arteriosclerosis; B. P. 180/110. Icterus index 12, serum proteins 5.9, A/G ratio 2.2	25	13	12	2
		3 w.	Brief phase of moderate dependent edema and moderate dyspnoea with few basal rales; B. P. 170/120. Icterus index 10, serum proteins 6.1 gm., A/G ratio 2.0	45	20	16	4
		1 mo.	No evidence of broken compensation; B. P. 170/100. Icterus index 10, serum proteins 6.1 gm., A/G ratio 2.2	25	14	..	2
PORTAL CIRRHOSIS							
9.	52	.....	Chronic glomerulonephritis with hypertension; mild icterus; no edema or ascites; ambulatory	45	15	..	1
		2 mo.	No ascites; mild dependent edema; serum proteins 6.7 gm., A/G ratio 1.9	70	21	..	3
		15 d.	Complete rest, no medication; no edema	35	16	..	1
10.	49	.....	Hypertensive cardiovascular-renal disease; compensation apparently intact; early cirrhosis, secondary to hepatitis 4 years previously	30	15	..	2
		3 mo.	48 hours after auricular fibrillation of 24 hours duration	60	19	..	2
		4 d.	Digitalized	40	16	..	2
		1 mo.	No medication; no evidence of circulatory embarrassment	40	15	..	2
11.	36	.....	Mitral stenosis, compensated; intermittent icterus; no ascites	35	18	12	1
		5 mo.	Compensation intact; continued intermittent icterus; no demonstrable ascites but superficial venous anastomoses more prominent	40	18	12	1
12.	42	.....	Essential hypertension; B. P. 210/115; early cirrhosis with slight intermittent icterus up to index of 20 units	30	14	14	2
		3 mo.	Icterus constant; B. P. 205/115. Icterus index 18, serum proteins 5.2 gm., A/G ratio 1.2	45	14	..	0
		7 mo.	Icterus index constant 22 to 24 units; B. P. 220/120. Serum proteins 4.8 gm., A/G ratio 0.8; possible slight ascites	55	18	16	0
13.	56	.....	Generalized arteriosclerosis, early cirrhosis. B. P. 155/95. Slight jaundice, no ascites. History of alcoholism	30	14	10	2
		5 mo.	Intermittent jaundice with icterus index up to 24 units; serum proteins 5.2 mg., A/G ratio 1.4	35	14	..	2
		6 mo.	Jaundice deeper, hemorrhage from esophageal varices. B. P. 170/110. Serum proteins 5.0; A/G ratio 1.0. Icterus index 23 to 28 units	55	22	16	0
14.	62	.....	Generalized arteriosclerosis; moderately advanced cirrhosis with peripheral anastomotic circulation; B. P. 160/95; constant mild icterus; no ascites	45	15	9	1
		3 mo.	Clinical condition essentially unchanged.	45	14	10	(*)

("Hep. Enl.") refers to palpable hepatic enlargement below costal margin in mid-clavicular line.

figures. It would appear in these 2 instances that hepatic regeneration and repair had proceeded normally regardless of the intercurrent circulatory insufficiency. In Case 6, on the other hand, in which significant decreases of dye excretion were precipitated by exercise tolerance studies, it is possible that the inception of exercise effected the change through the medium of either factor; that is to say, through either the induction of an hepatitic relapse or an untoward circulatory strain, or, possibly, both. All findings in the case were at a relative standstill approximately 6 months after the onset of the acute phase of hepatitis, and it was felt that the patient was entering upon a chronic status at the time when exercise tolerance studies were begun; by the third day, there was perceptible increase of scleral icterus, the patient was mildly dyspneic on complete rest, temperature was normal, appetite decreased sharply, and general malaise and moderate nonproductive cough supervened. It was at that point that the bromsulphalein retention sharply rose from 25% to 55%, the hepatic size and tenderness increased, the circulation time shifted from 15 seconds to 20, and the venous pressure rose to a high normal level. It is quite possible that both circulatory and purely hepatic degenerative components played independent or interdependent roles in this episode. The return of all values to former levels after 1 month of bed rest might equally well have occurred as a result of improvement in either factor.

The 2 instances of metastatic carcinoma of the liver here cited appear to reflect almost wholly the influence of circulatory decompensation on the bromsulphalein test. In each instance of this comparatively slowly progressive process, the significant alteration of dye retention coincident upon break in compensation was attended with parallel circulatory dysfunction as revealed by the circulation time and venous pressure data, and all returned to their former corresponding levels with apparent restoration of compensation. At the same time, there was no evidence, clinically or in alteration of blood proteins, icterus index or other findings to indicate acceleration of hepatic damage or intercurrent hepatitis.

Cases 9 and 10 of the cirrhosis group were quite similar in displaying marked alteration of the bromsulphalein retention during phases of cardiovascular incompetence in which the clinical status of the cirrhotic process remained relatively unchanged. They too, reverted to their former levels of bromsulphalein retention, circulation time and venous pressure upon subsidence of the decompensation. On the other hand, Cases 12 and 13, in which no loss of compensation was known to have occurred over periods of 10 and 11 months, respectively, presented progressive failure of dye excretion which was attended with abnormal circulation time and venous pressure readings only when the cirrhotic process itself was far advanced and complicating factors such as ascites (Case 12) and hemorrhage from ruptured esophageal varices (Case 13) had entered the picture. Cases 11 and 14 were not followed over a sufficient period to have entered that phase, nor did either present any evidence of circulatory breakdown during the period of observation.

In general, therefore, it may be said that the series here described gives concrete evidence of both factors concerned in the mechanism of bromsulphalein retention,—hepatic excretory dysfunction and circulatory inadequacy. As previously mentioned, there does not appear to be any present method for delineating the proportion of influence to be assigned to each factor where both are operative in the same patient. However, the data suggest the advisability of performing studies of circulatory integrity in those cases of liver disease in which there is clinical evidence of concomitant cardiovascular involvement. While it is evident that those instances in which such circulatory studies are abnormal will fail to indicate the proportion of abnormal dye retention due to either factor, it is equally true that

those in which circulation time and venous pressure are normal will present confirmation that the abnormal bromsulphalein retention can then be attributed solely to hepatic dysfunction. It is, therefore, suggested that in the performance of the bromsulphalein test in cases of hepatic disease occurring in the presence of coexistent cardiovascular abnormalities, the circulation time, with or without venous pressure readings, be determined, with a view either to ascertain possible circulatory factors in the retention of the dye or to establish the essentially hepatic nature of the dysfunction; such a study may further provide a basis for the evaluation of subsequent changes in either aspect of the patient's progress as determined by repetition of the tests at appropriate intervals.

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MENOPAUSAL HYPERTENSION: A CRITICAL STUDY

By R. D. Taylor, M.D.

A. C. Corcoran, M.D.

AND

Irvine H. Page, M.D.*

(From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Indiana)

The female menopause, whether natural or artificial, has long been regarded as a cause of arterial hypertension and the concept of "menopausal hypertension" has gained wide acceptance. Yet the evidence on which this view is based is largely derived from accumulated impressions rather than systematic study. With this in mind, we undertook the care of 200 menopausal women, 179 of whom had been surgically castrated and all of whom desired relief of menopausal symptoms.

Examination of the patients was conducted in such a way that a careful record was kept of both physical and mental abnormalities. Hypertension was considered present if any reading exceeded 149 mm. Hg systolic and 94 mm. diastolic. Some of the patients were treated with estrogens, thyroid substance, or the two combined. Others received sedatives, placebos and reassurance.

If lack of ovarian secretion were truly a cause of increased arterial pressure many of these patients would manifest arterial hypertension. Since most of them were young, the problem of analysis was not complicated by their having reached the age when hypertension would in any event be present in at least a quarter of the group.[1]

Results. The results of this time-consuming investigation can be summed up very briefly (Table 1). One hundred seventy-nine of the 200 women were castrated and the remaining 21 had clear evidence of ovarian failure. The ages ranged from 20 to 59 years. Thirteen per cent exhibited arterial hypertension, but 10% had shown this before the menopause. The hypertension was not more severe after the menopause than before in any of our patients, despite the emotional disturbance associated with the syndrome.

Thus only 6 patients of the 200 developed hypertension following the menopause and 5 of these were 40 years of age or older. These patients had long histories of psychoneurotic manifestations preceding the menopause. Eighty-three per cent of these were equally common among the younger castrates and among the older patients with natural menopause. Most of the symptoms attributed to the menopause were in fact intensifications of former neurotic trends.

The vasomotor phenomena described as characteristic of the menopause were not always easily evaluated. In some, flushing was observed on occasion but usually only the history of hot flashes was obtainable, and this often dramatized by the patient's own beliefs about the climacteric. Yet these very phenomena have probably been partially responsible for the view that the menopause plays a part in the genesis of hypertension. Vasomotor instability as expressed by flushing, chilly sensations, tachycardia and perspiration, while often associated with elevations in arterial pressure, is by no means a constant accompaniment. It is easy to convince oneself of this by observing the constancy of arterial pressure during a bout of flushing or supposed "hot flash." Further, these complaints were equally common among hypertensive and normotensive persons. Clearly so-called menopausal vasomotor instability, unless otherwise defined, need not neces-

* Present address, Cleveland Clinic Foundation, Cleveland, Ohio.

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* Present address, Cleveland Clinic Foundation, Cleveland, Ohio.

sarily be indicative of pathologic change in arterial blood pressure.

Discussion. Hypertension was present in 13% of the whole menopausal group, which agrees with the 14.7% given for normal workers in the statistics of The Heart Council of Greater Cincinnati.[2] Twenty per cent of our patients over 40 years of age had hypertension compared with 23.4% of the workers examined in Cincinnati. Clearly there was no increased incidence of hypertension in our patients with either artificial or natural menopause.

benefited by estrogen administration and in many cases not helped at all. Such treatment tended rather to distract the physician from concern over the more probable cause of the symptoms. This applied to both the surgically castrated patients and those with natural menopause.

Summary. A study of 179 castrated women and 21 with the natural menopause demonstrated that arterial hypertension is no more common in them than in the general population. "Vasomotor instability" as exhibited by "hot flashes,"

TABLE 1.—INCIDENCE OF HYPERTENSION AMONG 200 WOMEN AFTER THE MENOPAUSE

Age Groups	20–29	30–39	40–49	50–59	Total
Number of Cases	23	73	83	21	200
Natural Menopause	0	3	14	4	21
Surgical Menopause	23	70	69	17	179
Similar Premenopausal Hypertension	1	3	11	5	20
Hypertension Following Menopause	0	1	2	3	6

TABLE 2.—INCIDENCE OF ARTERIAL HYPERTENSION

Among 200 Women After Menopause

Age Group	No. Examined	No. with Hypertension	Per cent
20–29	23	1	4.3
30–39	73	4	5.4
40–49	83	13	15.7
50–59	21	8	38.0
Total	200	26	13.0
Above 40 years	140	21	20.2

Among 2860 Office, Industrial and Factory Workers

Age Group	No. Examined	No. with Hypertension	Per cent
20–29	727	62	8.5
30–39	1033	103	10.0
40–49	728	150	20.6
50–59	372	107	28.7
Total	2860	422	14.7
Above 40 years	1100	257	23.11

Administration of estrogens to menopausal patients with hypertension may aid in reducing the level of blood pressure, presumably by relieving some of the emotional tension, but its effects seem largely of secondary importance. The same degrees of blood pressure reduction are often observed by understanding management of the patient, or by administration of placebos or both.

When the syndrome was preceded by the neurotic symptoms, the menopause seemed to accentuate them. Patients suffering from severe neurosis were least

perspiration, and tachycardia, are not necessarily associated with hypertension and their alleviation by estrogens need not affect arterial pressure. The menopause seemed to intensify pre-existing psychoneuroses. Despite severe neurotic behavior, hypertension did not develop within three or more years except in 6 of these subjects. From these data it is concluded that the relationship of the menopause and hypertension is incidental and loss of ovarian secretion is neither a primary nor a contributory cause of arterial hypertension.

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AMYLASE LEVELS DURING MUMPS

THE FINDINGS IN BLOOD AND SALIVA

BY IRVING J. WOLMAN, M.D.*

BARNETT EVANS, C.PH.M.†

SIGMUND LASKER, PH.M.1/C†

AND

KENNETH JAEGGE, PH.M.3/C†

SHEEPSHEAD BAY, BROOKLYN 29, NEW YORK

(From the United States Public Health Service Hospital)

THAT mumps can raise the serum amylase has been known for a long time[2,4,7] but only in the past few years have the diagnostic possibilities been explored.

Murphy, Bozalis and Bieri,[8] in 1943, described 58 tests made on 35 patients with mumps. Elevated values were found in all but 7 tests, and 4 of these were from patients in whom preceding determinations had been abnormal. Fennel,[5] in 1944, reported increased amylase in blood and urine of an unspecified number of cases. Zelman,[11] in 1944, recorded the serum amylase of 89 hospitalized soldiers. On admission the levels were high in three-fourths of the group and normal in the rest, but by discharge, 2 weeks or more later, only 9% were still elevated. Of the group, 13 exhibited symptoms referable to the pancreas.

Applebaum,[1] in 1944, reported increased serum amylase in 45 of 50 patients. Curves made from the data suggested that the level rises early in the attack, stays up for a week or more during the active phase, and then subsides gradually as the swellings disappear. The author suggested that in bilateral parotitis the blood amylase may attain a higher level and maintain it longer than in unilateral disease. Haerem,[6] in 1945, described elevation of blood amylase in 9 adults with mumps parotitis.

Candel and Wheelock[3] similarly noted that of 224 adult males with mumps more than 96% showed elevations of serum amylase during the course of the disease. About 84% of tests showed elevated values in the 1st week of illness, and the proportion fell progressively to 27.5% by the 4th week. They found that the complications of orchitis and epididymitis did not affect the amylase levels. Parallel estimations of serum lipase failed to show hyperlipasemia as occurs in acute pancreatitis. They concluded that the elevations of serum amylase are associated with parotid involvement, for the reason that such elevations have also been demonstrated after ligation, calculous obstruction, or suppuration of the parotid ducts or glands.

In the studies here reported attention has been concentrated upon the relationship between serum amylase activity and (1) day of disease, (2) gland or glands involved, and (3) level of amylase in the saliva.

SUBJECTS. The subjects of the study were 101 adult males, members of the Coast Guard and Maritime Services. All were hospitalized between February 21 and May 8, 1945, during an epidemic, having been referred for admission as soon as the existence of mumps was recognized. Prior to the onset of this illness all had been in apparent good health; 25 were 17 years of age; 37, 18 years; 8, 19 years; 5, 20 years. The ages of those above 20 extended rather evenly to the 34 year figure. The patterns of glandular involvements and extraglandular compli-

* Surgeon (R), United States Public Health Service.
† United States Maritime Service.

cations were representative of what takes place in any typical outbreak of mumps. The symptoms, constitutional reactions and local inflammatory signs varied independently in severity from mild to severe.

A group of 47 "normal" controls of the same age distribution was set up as a standard of comparison for the blood determinations. This group was made up of healthy pharmacist's mates and of patients convalescent from non-abdominal infections such as scarlet fever or pneumonitis, or undergoing treatment for non-febrile genito-urinary ailments. One to 2 controls were tested with every batch of specimens from the mumps cases.

PROCEDURE. The blood specimens were collected in a dry tube in the morning, before breakfast, to avoid chylous clouding and hemolysis. The salivary specimens were also collected before breakfast. The patient's mouth would receive a preliminary rinsing with 0.6% sodium chloride solution, and then paraffin would be chewed. The saliva, which soon began to flow, was diluted at the bedside to 1:100 dilution with a Sørensen buffer of pH 6.8, and kept chilled until tested.

The tests of blood and saliva were carried out with the standard Somogyi[9] starch iodine procedure, modified to permit 1 technician to perform many tests quickly within a limited period of time. The main modifications were the use of multiple pipettes within a constant temperature water jacket, the reliance upon the achromic rather than the erythrodextrin endpoint in the iodine starch reaction, and the recording of the readings in minutes directly rather than in computed "units." These deviations from the standard procedure are feasible only when the amylase activity is abnormally increased or in the high normal range. They do not lend themselves to exploration of enzymatic activity in the zones of low normal and subnormal.

In considering the results the reader must remember that they were secured with biologic reagents, and that the "time in minutes" is related to the hydrolytic changes exerted by 2 ml. of body fluid upon 8 ml. of a standard starch solution. The shorter the time for the starch iodine reactions to fade away, the greater the potency of enzyme in the test mixture.

Results. SERUM. *Normals.* Fifty-nine specimens from 47 healthy controls gave results which ranged from 6 to 13 minutes and beyond. Since all but 4 (93%) of these values were 7 minutes or higher, (2, 6 minutes; 2, $6\frac{1}{2}$ minutes), the dividing line between normal and accelerated amylase activity has been set at $6\frac{3}{4}$ minutes, the approximate locus of the 90% statistic.

Nine of the patients used as controls were being hospitalized for acute epididymitis or orchitis. Two of these had been through an episode of mumps some years earlier and 2 others were aware of prior local trauma. With the remaining cases, classified as "mumps, non-specific," no immediate cause was apparent. There were no accompanying signs or symptoms to indicate that the mumps virus was the etiologic agent, though that possibility must nevertheless be entertained. None had increased serum amylase.

SERUM. *Mumps Patients.* Amylase tests were performed on 702 separate specimens of blood collected from the 101 patients at different and successive stages of their illness. The number of tests per individual patient ranged from 1 to 12. The serum amylase was found augmented in the majority of specimens (Fig. 1). This augmentation was most prominent during the first 7 days of illness. The 2nd week saw a return to normal, in most instances, though even by 18 days a few blood levels were still elevated.

With most patients the blood amylase was already elevated by the time they reported to the hospital. Six patients, however, exhibited normal values in the 1st few days of the attack, with sudden increases becoming apparent a day or 2 later, though not until the 11th day in 1 instance.

Of the patients who received 2 or more blood tests only 6 failed to show any increase. One of these displayed bilateral

sublingual infection without recognizable involvement of any of the other salivary glands. Another, with multiple salivary gland swellings, was tested only on the 6th and 13th day of illness. A third was tested only on the 4th and 5th days. These 3 patients might have been found with an elevated blood amylase at other times during their attacks, had a greater number of tests more evenly spaced been performed. The remaining 3 negative reactors received 3, 5 and 6 tests, respectively, well distributed through their attacks.

and lay in the same range as the corresponding values for the "mixed" multiglandular patients.

In 1 patient the mumps involved but 1 submaxillary and the right testicle. In another the swelling was restricted to the sublinguals. Neither of these non-parotitis patients, in 2 tests performed with each, displayed any elevation of serum amylase.

Thirty had scrotal swelling from involvement of 1 or both testes or epididymes. In 8 the onset took place while the salivary glands were actively swollen.

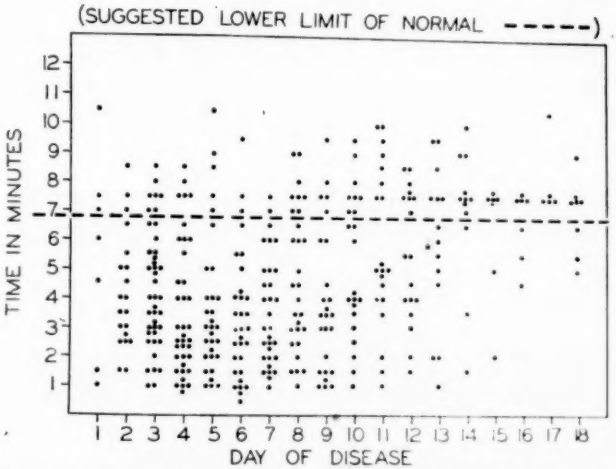

FIG. 1.—Distribution of 702 serum amylase determinations made on 101 patients in relation to day of disease. The trend of augmentation of the serum amylase level is most pronounced during the 1st week of illness, and then recedes steadily. (The shorter the time in minutes, the more potent the enzyme content of the serum.)

RELATIONSHIP TO SALIVARY GLANDS AND SCROTAL SWELLINGS. The great majority of the subjects had involvement of the parotids, 1 or both, some time during the course of the attack. One or more of the other salivary glands were usually swollen also. "Mixed" swellings were the rule.

There were 8 patients with parotid mumps in whom the involvement was unilateral, and 11 in whom the involvement was bilateral. The average and range of variation in serum amylase between the unilateral and bilateral groups were not significantly different from each other,

These 8 had elevated serum amylase, save for the 1 individual whose facial swelling was limited to the left submaxillary. In the other 22 cases, the scrotal swellings reached a peak after the glandular swellings had begun to subside. In 16 of these (73%) the serum amylase had returned to normal or was on the way down while the scrotal structures were still actively affected.

These latter observations suggest that the source of the elevated serum amylase in mumps is not the inflamed testicular or epididymal tissue. This supposition receives confirmation from the findings in

the 7 "control" cases of orchitis of traumatic or unknown origin, in whom the serum amylase level was well within normal bounds.

SALIVA. The salivary content of amylase was determined coincidently with the serum level in 97 tests of 55 patients, and in 33 tests of 33 controls (Fig. 2).

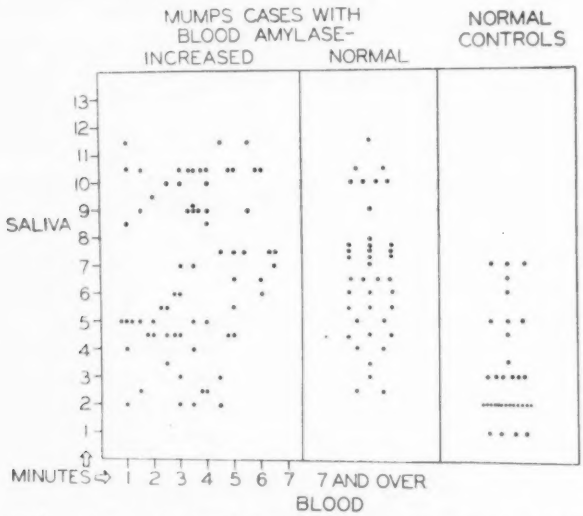

FIG. 2.—Graphic presentation of the correlations between the amylase level of serum and saliva as determined simultaneously in 97 tests with 55 patients. The values for the saliva of the control group themselves within a somewhat lower (and therefore more potent) range than do the values of the mumps patients, with or without increase of the blood serum amylase.

Each group of values exhibited a broad scatter. There were no evident correlations between serum amylase and saliva amylase. The amylase content seemed a little higher in the saliva of controls than in the mumps patients. This suggests that in mumps the content of diastatic enzyme in fasting saliva may be depressed.

Comment. These studies offer no confirmation to the hypothesis of Dunlop[4] that the augmentation of serum amylase in mumps is produced by parenchymal pancreatic involvement. None of our patients complained of gastro-intestinal or upper abdominal symptoms, even though mumps pancreatitis often appears during epidemics.[6,10]

It seems more reasonable, as most workers have pointed out, that the source of the increased blood amylase in mumps is the infected salivary gland system. Of the 3 sets of salivary glands, the parotids are both the chief producers of salivary enzymes and the glands most commonly attacked by the virus. That the submaxillaries and sublinguals are less responsible for the blood elevation is indicated by our observation that 1 instance of pure submaxillary involvement and 1 instance of pure sublingual involvement failed to develop any increase in blood amylase. In Applebaum's series,[1] similarly, when the disease of the salivary glands was exclusively extraparotid, as in 2 cases of submaxillary and 1 of sublingual inflammation, the amylase was normal.

Summary and Conclusions. 1. An analysis is presented of 702 serum amylase tests carried out on 101 adult males ill with mumps.

2. An elevation of the serum amylase level was nearly always present in the 1st week of illness. This increase usually faded away by the end of the 2nd week, though in several patients it was still increased in the 3rd week. Estimation of serum amylase is therefore of value as a

confirmatory test for mumps, especially with jaw swellings of obscure nature.

3. No relationship was noted between unilateral and bilateral gland involvement and the extent of the amylase increase.

4. No correlation was detected between serum and salivary amylase in random specimens of saliva. The saliva amylase seemed slightly lower in the mumps cases than in the controls.

5. The evidence suggests that the increase in serum amylase comes from the inflamed parotids, rather than from the submaxillary or sublingual glands, the pancreas, or the scrotal structures.

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THE FAILURE OF MASSIVE SALICYLATE THERAPY TO SUPPRESS THE INFLAMMATORY REACTION IN RHEUMATIC FEVER*

By T. N. Harris, M.D.
PHILADELPHIA, PENNSYLVANIA

(From the Children's Seashore House for Invalid Children, Atlantic City, N. J., The Philadelphia General Hospital, and The Children's Hospital of Philadelphia (Department of Pediatrics, School of Medicine, University of Pennsylvania)

Salicylates have been used in the treatment of rheumatic fever in 2 ways: as symptomatic treatment and in an attempt at specific therapy.

For symptomatic treatment in this disease the salicylates are very useful. Given in adequate doses during polyarthritis or high fever, they are very effective antipyretics and analgesics. The analgesic effect of salicylates in the arthritis of rheumatic fever is indeed so rapid that its effect is occasionally taken as a therapeutic test in the differential diagnosis of the arthritides.

The present study is concerned with the other use which has been advocated for salicylates in rheumatic fever, that of massive salicylate therapy with the object of a specific antirheumatic effect. The advocates of this mode of treatment have claimed the advantages of a shorter period of rheumatic infection and reduction in the severity of carditis. The suggestion of prolonged treatment of rheumatic fever by large doses of salicylates is not new, nor is the belief that such doses provide a specific treatment for the rheumatic process. As long ago as 1903, Lees suggested doses as high as 300 gr. of salicylate daily[6] to obtain a "true anti-rheumatic effect."[12] In 1906 Clarke reported the treatment of rheumatic patients with 240 gr. of sodium salicylate per day, and felt that this shortened the duration of the disease and protected the heart.

Recently the proposal of massive salicylate therapy of rheumatic fever has been revived in a paper by Coburn,[5] with the rationale that such doses of salicylates apparently suppress the inflammatory reaction of the host and thus tend to protect the heart from damage. As a result of this report, massive salicylate therapy has been adopted for rheumatic fever in a number of clinics, either experimentally or as an accepted procedure.[1,14,23,25,26]

It appears important to consider the advisability of massive salicylate therapy for the following reasons: 1. The results presented by Coburn in his paper advocating such treatment, and in the reports of 2 subsequent attempts to confirm his results, are not unequivocal. Coburn's report of the clinical results of massive salicylate therapy deals chiefly with the shortening of the period of infection in patients so treated, as judged by the erythrocyte sedimentation rate. The effects of this treatment on cardiac complications are given in the statement that "in none of 38 patients treated by this method did valvular heart disease develop, while in 20 to 63 patients receiving only symptomatic therapy there developed physical signs of heart disease." The cardiologic criteria used are not presented for valvular heart disease or for physical signs of heart disease. His patients were young adults of 18 years or more, and in this age group cardiac manifestations and residua of rheumatic disease are less common and less severe than in children. Manchester[14] also treated in this way a group of patients in naval service. He found a smaller number of significant cardiac residua among patients given massive salicylate therapy than among controls, especially if the therapy was instituted before "signs of significant carditis" had appeared. Fulminating infections did not always respond favorably, and there were 2 deaths in the intensively treated

* This work was supported by a grant from the Life Insurance Medical Research Fund.

group, on the 4th and 7th days, respectively.

Taran and Jacobs[23] gave massive doses of salicylates at the onset of rheumatic carditis to 8 children and treated 41 control patients in other ways. They concluded that "while it cannot definitely be stated that massive salicylate therapy unequivocally suppresses the rheumatic process and prevents the stigmata of heart disease, it is clear that this form of treatment makes the patients symptom-free." Wégria and Smull[26] gave 21 patients massive salicylate therapy, with 19 control patients. They concluded that the course of acute rheumatic fever is not shortened by massive salicylate therapy, with the reservation that earlier institution of treatment might have resulted in shortening the rheumatic episode.

2. Toxic reactions to high concentrations of salicylate in the blood are quite common. Tinnitus, nausea and vomiting are among the earlier toxic manifestations of salicylates. More severe manifestations have been reported, both as a consequence of massive salicylate therapy and otherwise. They include hypoprothrombinemia and hemorrhage,[8,17,18,24] occasional mental changes,[13,26] temporary deafness,[25] and some decrease in alkali reserve.[8,10] Moreover, 5 patients given massive salicylate therapy intravenously for acute carditis died,[1,14,23] either as a result of toxicity of salicylates or of failure of the treatment of carditis.

3. There have been indications in the recent literature that salicylates may lower the sedimentation rate without relation to activity of the rheumatic process. Rapoport and Guest[18] showed that in 10 of 15 patients with elevated erythrocyte sedimentation rates (ESR), 4 of whom had rheumatic fever, the ESR decreased following salicylate therapy. When this treatment was discontinued the ESR often began to rise toward its initial level. They also showed a decrease in the concentration of fibrinogen in the blood of these patients, and suggested that this might be due to an effect of salicylate on the liver. The latter has been suggested elsewhere as the basis for the hypoprothrombinemia caused by the salicylates.[19] Homburger[11] reported similar results in patients whose elevated ESR was, in fact, not caused by an infectious disease at all, but by carcinomatosis.

These indications of a non-specific effect of blood salicylates on the ESR are important for several reasons: (1) in all 3 clinical studies mentioned above the ESR was used as the criterion of the presence of an infectious process; (2) the fall of the ESR in massive salicylate therapy was offered by Coburn as evidence of specific suppression of the inflammatory process by the drug; finally, massive doses of salicylates may interfere with the reliability of the sedimentation test, which is usually the most sensitive indication of persistent rheumatic activity.

For the above reasons, and because adequate clinical testing of the effect claimed for massive salicylate therapy would require a prolonged study, it seemed particularly advisable to examine the rationale put forth as the basis of such treatment: that high concentrations of salicylates in the blood suppress the inflammatory reaction in rheumatic disease.

The hypothesis that salicylates suppress the inflammatory reaction in rheumatic fever has been tested in 1 study thus far. Murphy[16] observed 12 rheumatic patients under massive salicylate therapy with special interest in phenomena indicating inflammatory activity. The size of inflamed joints was determined frequently, and the skin temperatures over these joints were compared with the rectal temperatures. The ESR was also determined. The results of these measurements did not indicate any subsidence of the inflammatory reaction under the influence of massive salicylate therapy. In addition, Murphy observed in patients receiving this treatment such phenomena as fresh rheumatic nodules and, in 1 case, fresh polyarthritis and electrocardiographic evidence of further cardiac involvement.

The studies reported here represent another approach to the question of whether salicylates suppress the inflam-

matory reaction in rheumatic fever or merely affect the ESR. Preliminary observations were made of the effect of salicylate on elevated ESR in non-rheumatic patients; thereafter, children with signs of active rheumatic carditis and leukocytosis as well as elevated ESR were studied during massive salicylate therapy.

Methods and Materials. The patients studied were in the wards of The Children's Seashore House for Invalid Children at Atlantic City and the Philadelphia General Hospital. Salicylates were given as enteric-coated sodium salicylate tablets or as acetylsalicylic acid. When salicylates were particularly poorly tolerated, sodium bicarbonate was added in equal dosage. The daily dose was divided into 6 equal portions, given every 4 hours, day and night. It was occasionally necessary to exceed a total of 1 gr. per pound per day, in order to attain blood salicylate concentrations[2] of 350 gamma per cc.

The ESR was obtained, as described elsewhere,[9] by determining the rate during the period of free fall of erythrocytes and correcting to a 45% packed red cell volume. Leukocyte counts were done at approximately the same time of day, in duplicate.

Results. *Preliminary Observations:* A group of non-rheumatic patients with elevated ESR was chosen for these determinations. The object of these observations was to confirm the reports mentioned above[11,19] that doses of salicylate such as those suggested for massive salicylate therapy in rheumatic fever can lower an elevated ESR non-specifically. Six patients with pulmonary tuberculosis were studied, through the courtesy of Dr. Harold Israel of the Philadelphia General Hospital, and 4 patients with rheumatoid arthritis. The period of administration of salicylate differed among these patients, according to the severity of their toxic symptoms. Figure 1 shows the observed changes in the ESR. The data are given in crude rates of fall, mm. per hour, since the correction for packed red cell volume was not in all cases available in this experiment.

Examination of Figure 1 shows that in all but 1 of the non-rheumatic patients during salicylate treatment the ESR fell. In 8 of the remaining 9 patients, the rate of decrease was of the order found in rheumatic subjects under such treatment.

These observations, and similar ones quoted above, demonstrated that the fall in ESR under massive salicylate therapy was not necessarily a manifestation of specific action of salicylates in rheumatic fever. They did not, however, offer evidence against antirheumatic action of salicylates in high doses, since there remained a theoretical possibility that salicylates thus administered might produce both results: a specific antirheumatic effect and a non-specific effect on the sedimentation of erythrocytes in other patients. An experiment was therefore planned which might offer some evidence as to whether the lowering of the ESR in rheumatic patients was an indication of suppression of rheumatic activity in those patients.

Since leukocytosis provides another general indication of the persistence of inflammation, it was decided to institute massive salicylate therapy in rheumatic patients who were so active as to show not only an elevated ESR but also persistent leukocytosis, and to study the results of this treatment. The number of patients suitable for this study was sharply limited by the following considerations: (1) the rheumatic process must be sufficiently active for leukocytosis to continue for a few weeks; (2) the white blood cell count of the patient must not be affected by salicylates *per se*, to the point of reaching normal limits; (3) the patient must not be severely affected by the toxic manifestations of large doses of salicylates. Patients who satisfied all these criteria were given courses of massive salicylate therapy. The specific object was to see whether any patients would show evidence of persistent rheumatic activity despite such treatment and despite the consequent lowering of the ESR. Five such patients were found. Figure 2 shows some of the features of the clinical course of these patients.

From the clinical charts in Figure 2 it

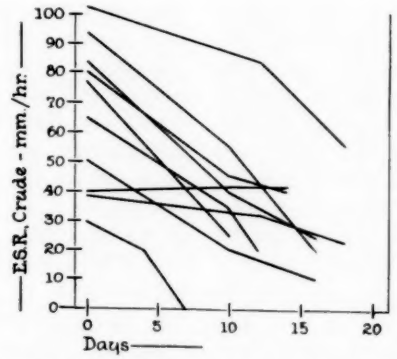

FIG. 1.—The fall in erythrocyte sedimentation rate in non-rheumatic subjects during massive administration of salicylates.

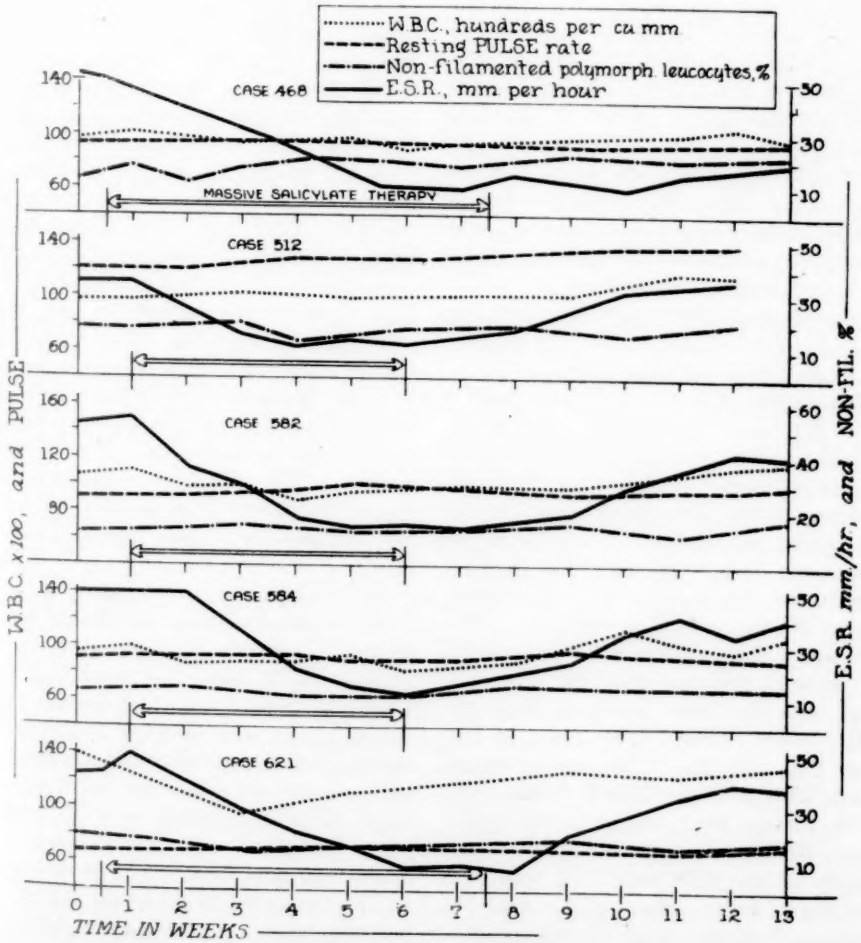
W.B.C., hundreds per cu mm
Resting PULSE rate
Non-filamented polymorph. leucocytes, %
E.S.R., mm. per hour
CASE 468
MASSIVE SALICYLATE THERAPY
CASE 512
CASE 582
CASE 584
CASE 621
W.B.C. x 100, and PULSE
E.S.R. mm./hr., and NON-FIL. %
TIME IN WEEKS
0 1 2 3 4 5 6 7 8 9 10 11 12 13

FIG. 2.—Clinical charts showing continued evidence of rheumatic activity, while the sedimentation rate is depressed by massive salicylate therapy.

is seen that the ESR in these cases reached normal limits, under the influence of massive salicylate therapy, while the white blood cell count still afforded evidence of continuing activity of the rheumatic process. The differential white blood cell count showed a shift to the left, or an abnormal number of non-filamented polymorphonuclear leukocytes, as additional evidence of a persisting inflammatory process. The resting pulse rate was elevated in 4 of the 5 cases, and in 2 of them the pulse rate showed a gradual rise over a period including that of the massive salicylate therapy. As to the clinical observations not charted, the following are relevant: (1) in no case was there a decrease in transverse diameter of the heart, or in intensity or transmission of murmurs during the period of salicylate therapy; (2) the vital capacity did not rise in any case during the period charted —in 1, Case 512, it fell from 0.8 to 0.5 liter; finally, no fever or polyarthritis was noted during the treatment, or any symptoms except those of salicylate toxicity.

In 4 of the 5 cases a definite rise in the ESR is seen to have occurred soon after the cessation of salicylate therapy.

Discussion. *The Comparative Sensitivity of the ESR and WBC Count.* Among the rheumatic patients studied during the past 5 years at these 2 institutions, 382 were observed during some phase of activity of the rheumatic process as indicated by laboratory tests. Of these, 328 patients were under observation until the quiescence of the infectious process. The laboratory data obtained in this group of patients indicate that the ESR, as used, was far more sensitive than the WBC count. Only in 6 cases, or less than 2%, did the WBC count remain above 8500 after the ESR had descended to the plateau level normal for that child. These findings on the comparative sensitivity of the ESR and WBC count in rheumatic fever agree with those of Ernstene.[7] If we accept the finding of a shift to the left in the peripheral blood as having the same implication as leukocytosis these findings agree also with Rogatz[20] and with Struthers and Bacal.[21] There is an apparent disagreement between these comparative data and those of Massell and Jones,[15] and Wilson.[27] These authors found the ESR and WBC count of approximately equal sensitivity as indications of an inflammatory reaction, but this apparent disagreement is probably due to the standards used. Massell and Jones, and Wilson, considered as normal any corrected ESR of 0.38 mm. per minute (23 mm. per hour) or less, since that value is approximately the upper limit of normal for the population. There is, however, a wide range of individual variation in the ESR, and the normal values of some subjects may be as low as one-fifth the upper limit of normal for the entire population. In the case of a convalescing rheumatic patient seen for the first time in the acute stage of the disease, it is not possible to decide whether the patient's normal value has been reached when his ESR has fallen to the upper limit of normal for the population. Accordingly, in the author's laboratory, the ESR is considered normal for any given convalescent rheumatic when the falling curve of ESR *versus* time reaches a plateau. Used in this way, the ESR has been found to be far more sensitive than the WBC count as an indicator of persistent inflammation. This difference has been discussed because it considerably enhances the significance of the results reported here.

The Significance of the Data Presented. It should be noted that the clinical course of the 5 patients reported here is not typical of all those for whom massive salicylate therapy was instituted. Even among the patients selected for this study on the bases mentioned above it was found that in some the active rheumatic process began to subside shortly after the institution of massive salicylate therapy. In others, the depressing effect of salicylates on the peripheral WBC count, which has been described by other investigators,[21,27] sufficed to lower the count to the normal range, although there were other indications of continuing rheumatic activity.

The cases chosen for presentation were those in whom the clinical course and laboratory data permitted a demonstration of rheumatic activity during massive salicylate therapy.

This study constitutes no attempt to evaluate the effect of massive salicylate therapy in rheumatic carditis. Such an evaluation would involve prolonged study of patients in various categories of cardiac involvement. The purpose of this study has been to examine the hypothesis that massive salicylate therapy suppresses the inflammatory reaction in rheumatic fever, which is the rationale for this mode of treatment. The data reported here are inconsistent with this hypothesis, since they demonstrate that both general and specific evidences of rheumatic activity can be observed during massive salicylate therapy. The fact that such demonstration of continued rheumatic activity can be made at a time when the ESR is within normal limits as a result of such treatment, and the further demonstration that salicylates can lower the ESR in other states in the same degree as in rheumatic fever raises a question as to the significance of Coburn's observations on the basis of which the concept of massive salicylate therapy has been revived.

Summary and Conclusion. 1. Recently reported observations that large doses of salicylates may lower the erythrocyte sedimentation rate of non-rheumatic as well as of rheumatic patients have been confirmed.

2. The hypothesis that massive salicylate therapy suppresses the inflammatory reaction of the rheumatic patient has been tested by treating in this way patients in whom the rheumatic process is so active as to produce a prolonged leukocytosis. It has been found that, although the ESR is lowered to normal limits by such treatment, the leukocytosis may remain, although the latter is a much less sensitive indicator of inflammation. This finding is supported by a continued shift to the left in the differential blood count, and by specific signs of continued rheumatic activity, which were observed in the cases presented while the ESR was within normal limits as a result of salicylate treatment.

It is very doubtful, therefore, that massive salicylate therapy suppresses the inflammatory reaction of the rheumatic patient or that the lowering of the ESR in rheumatic patients so treated has the significance attributed to it by Coburn.

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CHANGES IN PERSONALITY APPRAISAL ASSOCIATED WITH A RESTRICTED INTAKE OF B VITAMINS AND PROTEIN

By Charles R. Henderson, Norman C. Wheeler, Howard C. Johnson, Robert C. Cogswell, Jr., and George H. Berryman
(From Army Medical Nutrition Laboratory, Chicago, Illinois, an installation under the jurisdiction of the Office of The Surgeon-General, U. S. Army)

Andrew C. Ivy and Theodore E. Friedemann
(From Department of Physiology, Northwestern University Medical School, Chicago, Illinois)

and

John B. Youmans
(From Civil Public Health and Nutrition Division, Preventive Medicine Service, Office of The Surgeon-General, U. S. Army, Washington, District of Columbia)

Personality changes have been reported to be part of the syndrome of clinical B complex deficiencies.[6] The symptoms of the "initial nervous syndrome,"[3] described as being associated with pellagra and other deficiencies, are as follows: "hyperesthesia to all forms of sensation; increased psychomotor drive; increased emotional drive with a definite trend toward depression and apprehension, weariness and increased fatigability; headaches; sleeplessness. In general, these patients appear to have anxiety states with depressive features."

The development of the *Minnesota multiphasic Personality Inventory* (MMPI) by Hathaway and McKinley[4] permits more objective measurement of such symptoms. The possibility arises that it may aid in earlier clinical detection of psychopathology associated with certain nutritional deficiency diseases. The *Inventory* is based on the classification by the subjects of 550 "key" statements as "true," "false," or "cannot say." Scores are obtained by comparing the answers with those obtained from patients having known neurotic and psychotic aberrations (depression, hysteria, hypochondriasis, psychasthenia, schizophrenia, hypomania, psychopathic deviate, male-female interest and paranoia). Increase in scores beyond the range designated as normal (30–70) indicates a deviation in the direction of abnormal personality.

The purpose of the present communication is to describe the changes in personality appraisal scores (MMPI) which occurred while 7 young men subsisted on a diet containing restricted quantities of the B complex vitamins (including the "lesser-known" factors, *i. e.*, pyridoxine, pantothenic acid, "folic acid" and biotin), and animal protein. Deviations toward the abnormal in certain categories, *i. e.*, *hysteria*, *hypochondriasis* and *depression*, were definite when compared with the scores made by the same subjects during the "control period," and reverted to "normal" with equal definitiveness upon adequate supplementation with the nutrients which had been provided earlier in restricted quantities. These deviations appear to be similar to those reported in analogous investigations by Keys and associates.[5] In addition, certain signs in other categories corroborated the changes which were indicated by the personality appraisal. These included the changed demeanor of the subjects that was apparent to all the observers, the marked contrast in demeanor between control and experimental subjects, a marked decrease in physical performance scores, and certain clinical signs, such as consistently high resting pulse rate and diastolic blood pressure.

Program. The subjects, environment, diet, etc., have been described in detail elsewhere.[2] In summary, 7 young male volunteers, aged 23 to 27, consumed a normal diet for 12 weeks, during which various measurements of physical and psychomotor performance were made in order to establish

normal or base line levels. Personality appraisals were made at the end of the normal diet period using the MMPI. Following this control period, an experimental diet which contained restricted quantities of B complex vitamins and animal protein was consumed by all 7 subjects for 5 weeks. The nutritive values of the normal and experimental diets are shown in Table 1, and a sample menu for the latter in Table 2.

TABLE 1.—NUTRITIONAL CONTENT OF THE NORMAL AND EXPERIMENTAL DIETS

Nutrients	*Normal diet*	*Experimental diet*
Calories	3170*	3300*
Protein (gm.)	70*	40
(l-Tryptophane) (mg.)	700–900	210–300
Calcium (gm.)	0.86*	0.20*
Phosphorus (gm.)	1.26*	0.58*
Iron (mg.)	15.50*	12.00*
Thiamine (mg.)	1.44	0.50
Riboflavin (mg.)	1.84	0.30
Niacin (mg.)	15.60	5.80
Biotin (mcg.)	44.00	19.00
L. casei factor (mcg.)	64.00	23.00
Pantothenic acid (mg.)	4.70	1.10
Pyridoxine (mg.)	1.70	1.10
Ascorbic acid (mg.)	105.00*	90.00*
Vitamin A (I.U.)	7400*	16,600*

* Calculated.

TABLE 2.—SAMPLE MENU OF EXPERIMENTAL DIET

Breakfast	*Dinner*
Applesauce	Baked hominy grits
Fried cornmeal mush	Hot beets
Fried salt pork	Perfection salad
Karo syrup with Maplene	Plain cornmeal muffins
Oleo	Oleo
	Cranberry sauce
	Apple Betty
Lunch	*Bedtime*
Baked spaghetti casserole with corn muffin crumb topping	Cornmeal muffins
	Grape jelly
	Lemonade
Green beans	Sugar
Carrots	
Pickle relish	
Plain cornmeal muffins	
Oleo	
Pear halves	

NOTE: Normal diet consumed by all subjects the first 12 weeks; thereafter all subjects, both control and experimental, consumed experimental diet but former received supplements in quantities to equal or slightly exceed levels of nutrients found in normal diet. Calcium, phosphorus and iron levels of the experimental diet were increased to 0.9 gm., 1.1 gm., and 32 mg., respectively, by use of dicalcium phosphate and iron pyrophosphate. Ascorbic acid content of experimental diet was provided in part by synthetic lemon powder fortified with ascorbic acid. Vitamin A content of experimental diet was mostly in the form of beta-carotene.

At the end of the 5 weeks, 2 of the subjects were chosen as "controls" and received crystalline supplements of the B complex vitamins and protein in amounts to equal or exceed the levels found in the normal diet.* Three of remaining 5 subjects began an additive supplementation schedule at the end of 15 weeks, and the remaining 2 at 18 weeks. The general plan of supplementation differed for the 5 subjects. Within a relatively short period of time following experimental week 15, Subject E–3 received all the supplements given to the control subjects. Subject E–4 was similarly supplemented except that the lesser known B factors (pyridoxine, pantothenic acid, *L. casei* factor and biotin) were given some time after thiamine, protein, riboflavin and niacin. The remaining 3 subjects received the supplements according to a step-wise additive schedule. During experimental weeks 36 to 39, all subjects consumed a luxurious diet, plus supplements of crystalline nutrients and 10 gm. daily of high vitamin potency yeast. The schedule for control and experimental subjects was as follows:

Diet and Supplementation. Control subjects (C–1 and C–2): Control weeks 1 to 12—normal diet. Experimental weeks 1 to 5—experimental diet. Experimental weeks 6 to 35—experimental diet plus full supplementation. Experimental weeks 36 to 39—luxurious diet in quantities desired individually.

Experimental subjects (E–3, E–4, E–5, E–6 and E–7): Control weeks 1 to 12—normal diet. Experimental weeks 1 to 15 (E–3, E–4, E–5), 1 to 18 (E–6 and E–7)—experimental diet. Experimental weeks 16 to 35 (E–3, E–4, E–5), 19 to 35 (E–6 and E–7)—experimental diet plus additive supplementation with crystalline B vitamins and protein.

* The supplements were as follows: (1) 40 gm. animal protein (as 45 gm. calcium caseinate); (2) 0.7 gm. calcium as dicalcium phosphate; (3) 0.54 gm. phosphorus as dicalcium phosphate; (4) 20 mg. iron as iron pyrophosphate; (5) 666 I.U. vitamin D; (6) 1.2 mg. thiamine hydrochloride; (7) 1.5 mg. riboflavin; (8) 12 mg. nicotinamide; (9) 60 mcg. biotin; (10) 90 mcg. *L. casei* factor (folic acid); (11) 6 mg. pantothenic acid, half as racemic calcium pantothenate and half as dextro calcium pantothenate; (12) 300 mcg. para-aminobenzoic acid; (13) 3 mg. pyridoxine hydrochloride; (14) 0.5 gm. choline chloride as choline dihydrogen citrate.

Experimental weeks 36 to 39—luxurious diet in quantities desired individually.

Personality appraisal was made on 4 occasions during the experimental weeks 1 to 39. At the same time numerous other measurements were made weekly or bi-weekly, for the physical, psychomotor, clinical and biochemical aspects.

RESULTS. Significant changes occurred in the triad: hysteria, hypochondriasis and depression. Reference to Figure 1 shows that at the second appraisal, following some 15 weeks of the restricted intake of nutrients, a rise in score was obtained for all 5 experimental subjects in these 3

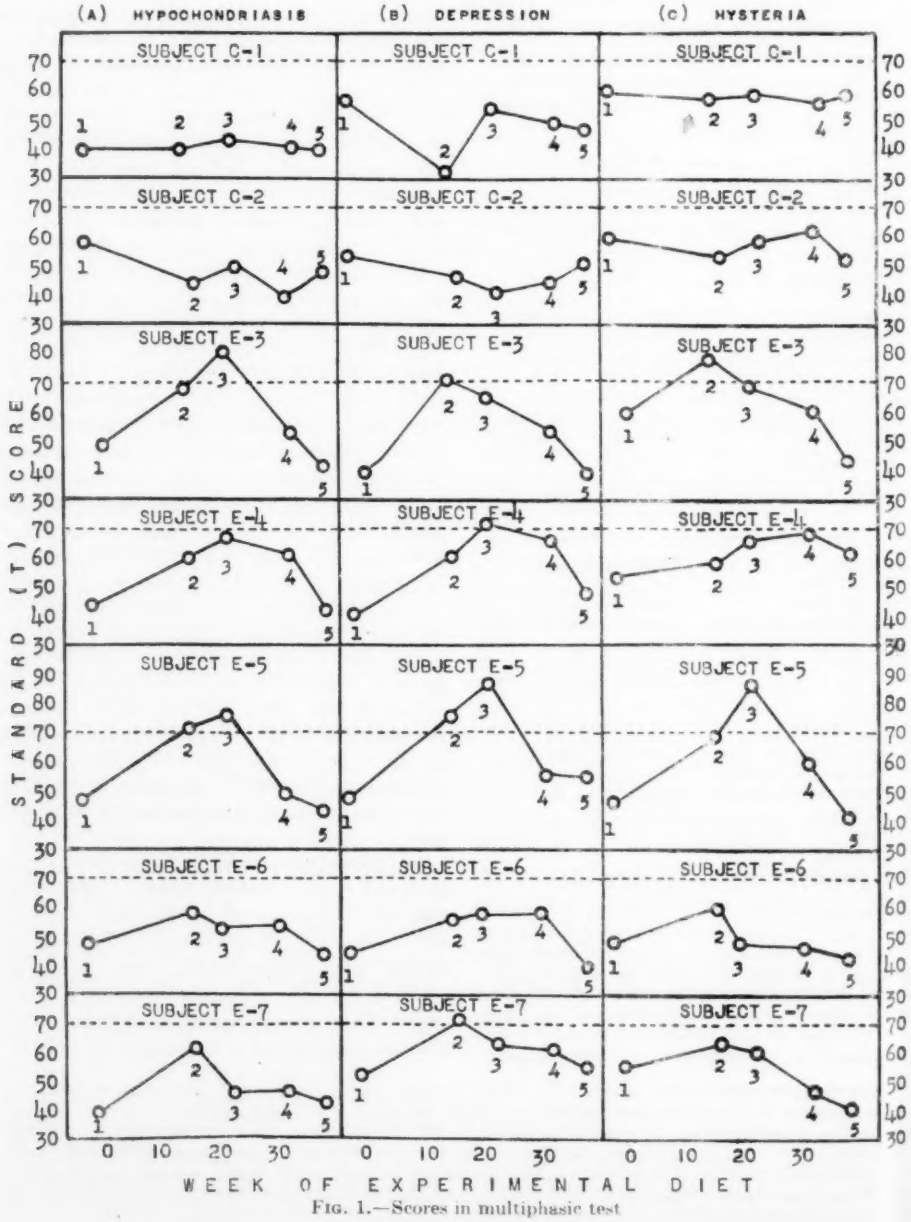

FIG. 1.—Scores in multiphasic test

personality categories, while the scores for the controls were either unchanged or decreased. Only a few of the increased scores made by the experimental subjects exceeded the normal *range*, however.

At the point of third appraisal, supplementation with thiamine had been given to all subjects, protein to Subjects E–3, E–4 and E–5, and niacin and riboflavin to E–3. The times at which the various supplements were received are shown in Figures 1 and 2. Following supplementa-

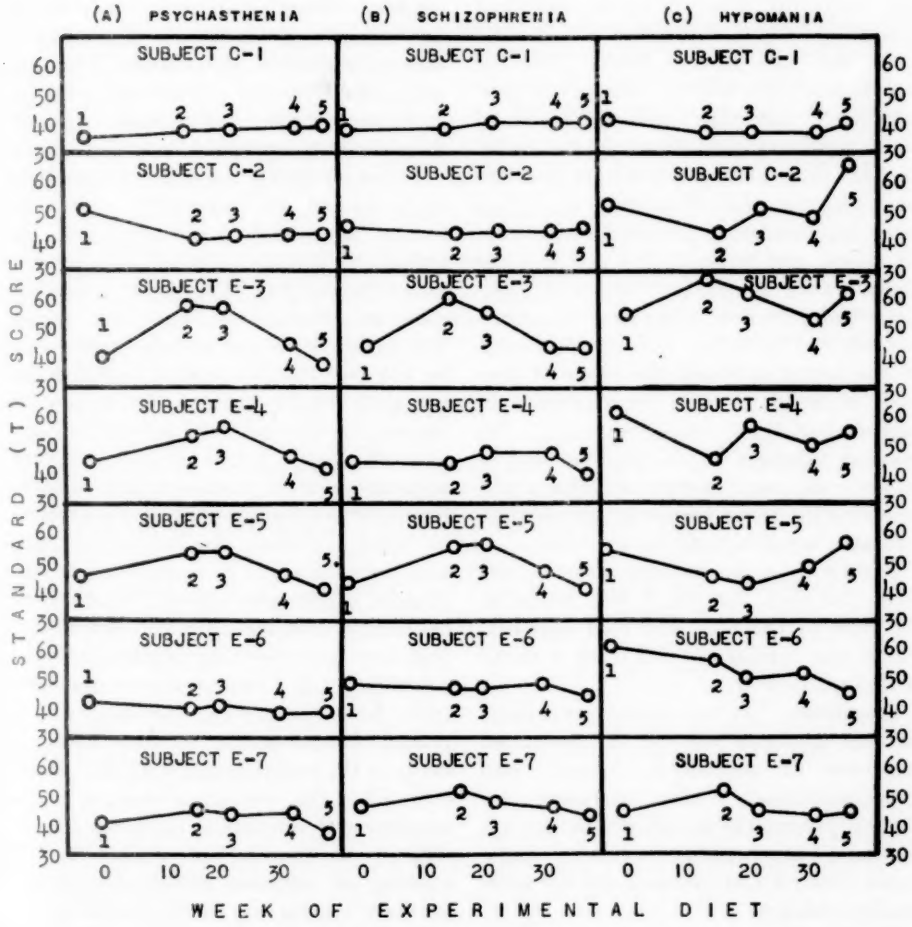

FIG. 2.—Scores in multiphasic test

Explanation of Figures 1 and 2: The normal range of scores on the multiphasic test is considered to be 30 to 70. The times at which the multiphasic tests were given are designated by the numerals *1*, *2*, *3*, *4* and *5*, corresponding to different dietary and supplementation régimes as follows: *1*, Just before change from normal to experimental diet. *2*, After approximately 15 weeks on experimental diet and just before supplementation of experimental subjects began. *3*, Following 6 weeks of thiamine supplementation and 1 week of animal protein, nicotinamide and riboflavin to E–3; following 6 weeks of thiamine supplementation and 1 week of animal protein, supplementation to E–4 and E–5; and following 2 weeks of thiamine supplementation to E–6 and E–7. *4*, Following 11 weeks supplementation with lesser-known B vitamins and 6 weeks of egg, meat and milk to E–3; following 6 weeks of egg, meat and milk, 6 weeks nicotinamide supplementation, 5 weeks riboflavin supplementation and 2 weeks lesser-known B vitamin supplementation to E–4; following 5 weeks nicotinamide and 4 weeks riboflavin supplementation to E–5; and following 5 weeks protein and nicotinamide and 4 weeks riboflavin supplementation to E–6 and E–7. *5*, Following 2 to 3 weeks on a luxurious diet.

tion with thiamine, Subjects E–6 and E–7 showed slightly to moderately lowered scores representing lowered tendency to hysteria, depression and hypochondriasis, whereas the other 3 subjects presented in general higher scores, despite supplementation not only with thiamine, but also with the other nutrients described above.

At the time of the fourth test, the supplementation described above had been continued, and high excretion levels of those nutrients were found in the urine. By this time, other supplements had also been added so that all subjects were then receiving thiamine, protein, niacin and riboflavin, and Subjects E–3 and E–4 the lesser known B complex factors, in addition. Subjects E–5, E–6 and E–7 had not yet received the latter. At this point none of the scores exceeded the range of normal, although certain ones were still higher than those found originally. No marked difference in the improvement of scores was seen in those subjects not receiving the lesser known B complex factors as compared to those who did.

Return to approximately normal score levels for each individual was found at the time of the fifth and final appraisal which was carried out following 3 weeks of the luxurious diet.

Discussion. As mentioned previously, changes appeared only in the associated categories of depression, hysteria and hypochondriasis. Other categories including psychasthesia, schizophrenia, hypomania, psychopathic deviate, male-female interest and paranoia did not show decisive changes.

The described deviations in personality inventory substantiated the qualitative impressions of all observers concerned. Whereas the experimental subjects were languid, morose and occasionally irritable, it was necessary to request the control subjects to restrain their ebullient spirits in the interests of maintaining harmony in the group. Interesting alterations in resting pulse rates and diastolic pressures were found in the experimental subjects, these being considerably higher than the corresponding readings taken during the control period, and returning to normal upon supplementation. Concurrent decreases in physical performance were observed with the increases in personality appraisal scores. Similar but not so decisive decrements were observed in psychomotor performance. The physical and psychomotor test results, described in detail elsewhere,[2] indicate that changes in those categories accompanied changes in personality appraisal described herein.

In the interpretation of results, we have contemplated the possibility that such factors as monotony of diet and the tedium of routine physical and psychomotor testing may have played important rôles in causing the deviations noted. This possibility is not excluded completely by the fact that the control subjects did not show similar changes, for knowledge concerning who were the control subjects and who were not, eventually became apparent to all of them—in spite of withholding this information from the subjects by using the same diet for all, placebos that were identical in appearance to the vitamin supplement capsules, and identical testing techniques for all. Knowledge that they were receiving supplements conceivably could have prevented the controls from undergoing personality appraisal changes similar to those found to occur in the experimental subjects. However, when the reversal of changes in the experimental subjects is interpreted, it is difficult to conceive of similar factors exerting an influence during that phase, for there was no way for the experimental subject to know if, when, or how he received supplements. These were added either directly to the food without the subjects' knowledge, or given by means of a tablet or capsule that was the same in appearance as the placebos. The only remaining explanation would appear to be that the changes in well-being and physical performance were paralleled, more or less, by return to normal scores on the personality appraisal test.

Summary. During a period of restricted intake of B complex vitamins and protein, 5 subjects showed changes in personality appraisal (*Minnesota Multiphasic Personality Inventory*) that were coincident with changes in other categories, notably physical and psychomotor performance and resting pulse rate and diastolic pressure. The changes occurred in the triad of hysteria, hypochondriasis and depression, but not in any of the other categories included in the Minnesota multiphasic test. Similar changes were absent in the control subjects. With supplementation, there occurred a beginning regression towards scores found originally during the initial normal diet period. This improvement progressed during the course of supplementation with thiamine, protein, nicotinamide, riboflavin and the lesser known B complex factors, and was concurrent with improvement in physical performance and feeling of well-being. Actual attainment of each subject's original "normal" scores occurred following a final 3 week period when a luxurious diet was fed.

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PROGRESS
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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.

HERMAN BEERMAN, M.D., AND NORMAN R. INGRAHAM, JR., M.D.
EMERITUS PROFESSOR AND ASSISTANT PROFESSORS, RESPECTIVELY, DEPARTMENT OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA

VIRUS PYOGEN AND VIRUS PYOGEN PHOTOSENSITIVITY RELATIONSHIPS IN CUTANEOUS DISEASE

BY JOHN H. STOKES, M.D.
AND
HERMAN BEERMAN, M.D.
PHILADELPHIA, PENNSYLVANIA

AN interesting trend of the present day is the growing appreciation of causal interplay in the field of infective agents. Primary and secondary infection, not alone in the field of the bacteria, but as between fungi and bacteria, and viruses and bacteria, is gradually attaining what is evidently a deserved recognition; and bacterial allergy as distinguished from simple bacterial infection is serving increasingly to explain or provide plausible theory for a range of manifestations much broader than those produced by simple infection alone. Moreover, allergic interplay is now taken to include interplay between bacterial and other types of allergic response. Foods incite to exacerbation and relapse of infections, infections bring about allergic responses to foods; and now infections incite to allergic types of response to other infections, in sequences in which the primary offender is with difficulty identified, or perhaps has altogether disappeared in the commotion produced by the second organism participating in the infection-allergic sequence. Such infection-allergic sequences have been recognized in dermatology in the strepto-levurids for example, described by Darier, Ravaut, Ramel and their associates.[16] They are with good reason suspected in the fungus-pyogen dermatoses included in the colloquial term, "athlete's foot" and the eczematoid eruptions of hands and feet. It is the purpose of this review to cover the groundwork of still another type of sensitization sequence, the "virus-pyogen sequence" as we shall call it, recognition of which is on the threshold, so to speak.

Such a concept is of use in explaining 2 painfully common phenomena in dermatologic practice: relapse and non-cure for which no gross external mechanism such as reëxposure to a contact allergen, for example, can be demonstrated. Inflammatory eruptions of varied origin, including industrial and contact dermatitis with "eczematoid" or "infectious eczematoid dermatitic" characteristics, and persistence after removal of the primary irritant or allergen; and the pyogen complicated flares of acne vulgaris, dermatophytosis, lupus erythematosus, and the eczema asthma hay-fever complex ("prurigo Bes-

nier" and the so-called neurodermatitis disseminata) are cases in point. Without too much stretching, outright disease entities such as the varicelliform eruption of Kaposi can be grouped under these categories. Suspected virus diseases such as dermatitis herpetiformis, and the impetiginizing herpetic processes and bullous impetigoes seem less far apart; and drug eruptions very plausibly respond to interpretation by an approach to the Milian[47] formula of infection activation in which the drug merely stirs up a previously existing infection, or perhaps more currently, an infection allergy. The relationship between the sensitizing infection and its consequence is at times reversible, and a pyogenic infection may seem to sensitize to a virus as in the Kaposi eruption, or the 2 may coëxist, or, as we suspect more often, the virus paves the way for the pyogenic explosion, which follows it after a fairly well-defined incubation period or refractory phase, and completely overshadows the first offender. Moreover, it is not necessary that the sensitization be between agents on the same terrain, *e. g.*, the skin. The virus may be in the paranasal sinuses or the intestinal tract or distributed throughout the body in a general infection, and the primary or relapsing manifestations in a specialized skin structure such as the hair follicle. Or a small focal colony as at a tooth apex, disturbed, may act as a trigger for a wholesale herpetiform outbreak or an exfoliative dermatitic "drug eruption." As isolated cases or small groups, these occurrences have now been recorded in the literature, with but scant attention to their etiologic integrative possibilities. Collecting them raises their impressive value and provides a basis for further study.

The following tabulation groups a number of virus infections (or suspected virus infections) in which pyogen correlates have and have not been suspected.

The virus pyogen sequence in variola-vaccinia has been interpreted historically as a coincidence by many observers, interest being absorbed by the corpuscular or granular body studies of Guarnieri and Negri in their application to variola by Paschen.[51] The transmission of the disease by the bacteria-free fluids of the early vesicle quite overshadowed for a time the pyogen sequence. Arndt[3] in the Dresden epidemic of 1918–1919, however, found streptococci and pneumococci in the blood. Hines[30] in the Chicago epidemic of 1922 found both the hemolytic and non-hemolytic streptococci in the blood. Ikeda[31] in the excellent studies with Michelson[46] and Sweitzer[65] of the Minnesota endemic and epidemic smallpox, found that of 28 cases subjected to blood

TABLE 1.—VIRUS INFECTIONS AND PYOGEN CORRELATES

Pyogen correlate or sequence suspected	Pyogen correlate apparently absent
Vaccinia	Virus pneumonia
Variola	Virus hepatitis
Varicella-zoster	Encephalitis
Herpetic infections	Poliomyelitis
Herpes-impetigo (virus impetigo)	Ornithosis
Influenza	Mumps
Adult diarrhea, "food poisonings," etc.	Measles
Atypical diarrhea of infants	Rubeola
Nasorespiratory and bronchitic infections ("coryzal types")	Lymphogranuloma venereum
Aphthous uveitis	Verruca vulgaris
Acute infectious gingivostomatitis	Molluscum contagiosum
Ectodermosis erosiva pluriorificialis	Waelsch urethritis
Triple syndrome of Behcet	
Erythema multiforme	
Dermatitis herpetiformis	
Pemphigus	
Catarrhal vulvovaginitis	

culture, with the hemorrhagic form of the disease, 23 showed streptococci, 16 hemolytic and 7 non-hemolytic. Five were negative. In the discussion of Michelson and Ikeda's paper, Schamberg, whose experience with the disease was one of the largest, stated that though the fluid of the early variola vesicle is bacteria-free, by the 4th to the 6th day, streptococci are found both in the vesicles and in the blood. He recalled Councilman's statement that a patient does not die of smallpox *per se*, but of a streptococcic septicemia. Clinical observation of the course of variola does much to impress the belief that it is a syndrome of 2 infections, the viral stage including the appearance of the initial exanthem, and temperature rise, and the ensuing vesiculation, and the pyogenic invasion which produces the pustular manifestations, the secondary fever, the septicemic and hemorrhagic manifestations, abscesses, etc. Ikeda, however, insists from his study of the Minnesota material that the full-blown variola pustule is sterile, but the pustule with hyperemic reaction in the surrounding skin often yielded hemolytic streptococci.

What is evidently needed to amplify these suggestive observations is further study of pyogen susceptibility and pyogen flare reactions of persons with normal skins, following initial vaccination in variola epidemics, and of the behavior of the clinical pyogen-susceptibles with pustular acne, staphylodermias, etc., under similar circumstances.

The varicella-zoster relationship is still involved in controversy, chiefly as to the identity of the viral causes of the 2 diseases. We have been able to find little in the literature to suggest a virus-pyogen relationship in the clinical manifestations ascribed to the zoster virus, though Rosenow and Oftedal[54] thought they had reproduced zoster in animals by injecting streptococci isolated from various focal infections in patients suffering with zoster. Sunde[64] found diplococci and short coccal chains in the Gasserian ganglion of the affected side in a case of herpes zoster ophthalmicus. In contrast with the virus pyogen findings in herpes simplex, we have been unable to find any report of pyogenic invasion of the elementary zoster lesion. It would appear that a more intensive study of "complicated," *i. e.*, gangrenous zoster, and secondarily impetiginized otic ganglion zoster (a not uncommon clinical complication) is desirable.

The impetiginization of herpes simplex lesions is a matter of common clinical observation but has had relatively little intensive bacteriologic study. Clinical experience also bears out the observation that impetiginization of herpetic lesions varies from individual to individual, and at different times in the life history of the same person. Geniculate ganglion herpes seems notably more frequently complicated by an early and rapid pyogen invasion, while the opposite seems to be the case in ophthalmic herpes. Possibly the soil on which the herpetic skin lesion appears is the determining factor. The ear and particularly the almost intertriginous retroauricular surface in ears set close to the skull, is a notorious haunt of streptococci as witness Mitchell's[48] study of the streptococcal dermatoses of the ear. Fenton's[18] discussion of otic herpes zoster calls attention to the milder, eczematous type of eruptive manifestation in this disease, which may represent a pyogen invasion or sequence, and emphasizes the differential importance of pain in identifying the herpetic element in cases masked by the eczematous appearances. Thus it is more than suggested that one type of herpetic infection can underlie in certain cases a variety of clinical pictures ranging from the *porrigo scabida* or *impetigo scabida* of Alibert (the "French ear") to the *pityriasis streptogéne* of Haxthausen. Attention is also directed in these papers to the instrumentality of the draining ear of otitis media in providing a secondary inoculative source for impetiginous eczema of the canal and auricle. In cases in which no evidence of drum perforation past or present can

be found, the possibility of an activating otic herpes should not be lost sight of. Campbell[12] has commented on the symbiotic relation of virus and pyogen in the minor varieties of impetigo contagiosa and has even suggested that impetigo itself may be at bottom a virus disease.

The immunologic status of the herpes virus-pyogen involved skin also deserves more study. In 1934 Pacréau[50] reported the effect of a stock staphylococcus vaccine with anatoxin in reducing the size of zoster vesicles, preventing eczematization and relieving symptoms. Francois[24] in 1936 used "antistaphylococcus vaccine" successfully in subcutaneous injection near the site of the zoster eruption, and Fouassier[22] employed it both subcutaneously and intradermally. Godal[29] and Magrou a year later confirmed the reported favorable experience of the foregoing authors. Apparently no procedure for determining the grade of sensitivity of the zoster patient's skin to staphylococcus vaccine or toxoid was undertaken.

The Kaposi varicelliform eruption, most frequently observed as a complication of the eczematous phase of the eczema-asthma-hay-fever complex in our experience, is an explosive varioliform eruptive affair accompanied by high fever and sometimes septic symptoms, which has been studied earlier in relation to pyogen invasion and more recently, as virus culture techniques have improved, from the standpoint of the herpes virus. Jaquette, Convey and Pillsbury[33] briefly review the earlier literature since Juliusberg[34] in 1898 suggested that the characteristic umbilicate lesions were produced by *Staphylococcus aureus*. A number of the subsequent papers which recognized the presence of staphylococci rated them as incidental and not truly causal. Jaquette *et al.*, on the basis of clinical similarities, emphasize the possible primary etiologic agent as the vaccinia virus. Barton and Brunsting[6] classify a number of papers on the basis of staphylococcus, streptococcus and virus etiologic leanings. King[37] reported a case of Kaposi's varicelliform eruption which began as herpes zoster. A number of authors since Freund[25] in 1934 reported the finding of Guarnieri bodies in the lesions of Kaposi varicelliform cases have attempted confirmation of his observation without success. The frequent presence of pyococci was acknowledged, but their significance contested.

In 1944, Blattner, Heys and Harrison,[8] working on a case clinically reported by Lane and Herold,[40] identified a virus which they regarded as closely related to, or a strain of the herpes simplex virus, and discarded the previous theorization regarding the vaccinia virus. In 1945, Lynch and his co-workers[45] reported the finding of the virus of herpes simplex in a case of Kaposi varicelliform eruption. The source was not determined in this case, but 2 other cases followed herpes simplex in a parent of each of the children affected.

So far as the literature then indicates, the virus-pyogen relationship in this group of dermatoses ("eczema hepeticum" as Lynch and co-workers propose to call it) needs further study not only on the virus side but also on the typing, pathogenicity status and immunologic and allergic responses to the pyogens which have been identified. Jaquette *et al.* confirm Lynch *et al.*, and venture a step further in including the beta hemolytic streptococci and staphylococci they found, in the etiologic interplay.

The next group of possible virus-pyogen correlates on which a get-together is badly needed includes the following:

1. Rendu[53] and Fiessinger and Rendu:[19] a syndrome characterized by simultaneous inflammation of all external mucous surfaces coëxistent with a varicelliform later purpuric eruption of all 4 extremities.

2. Klauder:[38] ectodermosis erosiva pluriorificialis.

3. Stevens - Johnson syndrome:[57] "a new eruptive fever associated with stomatitis and ophthalmia. See most recently Kove,[39] Stevens-Johnson syndrome.

4. Baader:[4] dermatostomatitis.

5. Levine, Hoerr and Allanson:[44] vesicular pharyngitis and stomatitis.

6. Behcet:[7] recurrent genito-oral aphthosis and uveitis with hypopyon.*

7. Franceschetti, Valerio and Babel:[23] using the above designation.

8. Ketzenellenbogen:[35] using the above designation.

9. Curth:[15] using the above designation.

10. Scott, Steigman and Convey:[55] acute infectious gingivostomatitis.

11. Lever:[42] severe erythema multiforme.

The clinical resemblances among these conditions are readily apparent to the dermatologist. Franceschetti and his coworkers[23] have well summarized some of the relations under a virus etiologic hypothesis as follows: Recurrent aphthous uveitis "is indeed an independent disease defined by the development of periodic attacks, by its complex and characteristic symptoms and by its resistance to treatment. . . . Although a virus explains in a fairly plausible way (since its existence cannot be proved with certainty, the inoculations having failed to produce the disease) the aphthæ and uveitis, it is necessary to introduce another factor, which is the sensitization of the organism. This allergy, however, seems to be secondary, and not the initial cause of the disease." He then relates it to the allergic status of the ocular disorders associated with rheumatic states. Cavara[13] and Adamantiadis[1] separately reported blood cultures of mildly pathogenic staphylococcus from the blood stream and Weve[70] felt that the articular process in erythema nodosum was a manifestation of an allergic state against the staphylococcus. Ageloff[2] and Ginandes[27] separately report isolation of streptococci and staphylococci from the lesions. Gilbert[26] thought the eye lesions metastatic and the patient the victim of a low-grade sepsis. Cavara and Adamantiadis in the Stevens-Johnson syndrome, believed that a virus made the body more susceptible to the staphylococcus.

Thus far, then, the negative holds the stage in this group so far as pyogen and virus etiology is concerned, but the application of better techniques on both sides may establish either or both causes, or an interrelation between the two. An allergic or sensitizing relation has already been suggested.

It is not the purpose of this summary to go in detail into the problem of virus etiology or influence in dermatitis herpetiformis and pemphigus whose clinical relations to erythema multiforme on the one hand, and to the known septicemic clinical forms of "pemphigus" (butcher's pemphigus, acute septic pemphigus of infancy) are familiar to dermatologists. For a good review of the latter group especially reference may be had to Lever's paper on severe erythema multiforme. There exist, however, as Callaway and Sternberg's[11] study of bacterial allergy in dermatitis herpetiformis illustrates, good reasons for suspecting that a bacterial allergic state is an important element (in their case pneumococcus Type VII) which underlies or participates in the cause of dermatitis herpetiformis. Urbach and his associates[67] support the virus concept for both dermatitis herpetiformis and pemphigus, while O'Leary and Welsh[69] and Welsh[68] have supported the streptococcal etiology of pemphigus. Until the virus work is elaborated and confirmed and the possibility of a filter-passing streptococcus derivative (see Rosenow on poliomyelitis) studied, the problem of virus pyogen relationship in this group remains unsolved.

Virus-pyogen Correlation in the "Influenzal" Nasorespiratory and Gastro-intestinal Virus Infection Field. This part of our summary is essentially a use of analogy (a not too strong form of argument in itself) to shed light on virus-pyogen relationships in the "exacerbative" group of dermatoses, which will be last considered.

The group of virus infections constituting so-called "influenza" has long been

* Attention should be called to the recent description of epidemic keratoconjunctivitis associated with seborrheic dermatitis. O'Donovan and Michaelson, Brit. J. Ophthal., **30**, 193, 1946, and Editorial, Brit. Med. J., 145, January 25, 1947.

recognized as having a definite cutaneous eruptive phase which was well summarized by Derbandiker[17] in 1933. From a survey of the literature and his own experience he described efflorescences ranging from roseola to varioliform pustular and erythema nodosum lesions associated with the febrile stage of the infection, and terminating promptly with the return of the temperature to normal. These "toxic erythemas" might be regarded as comparable to the roseolar phase of variola in the initial febrile stage. These are to be regarded as separate for discussion purposes from the sequential pyogenic manifestations which usually followed after an interval of several days, the virus infection as such. During the 1918 to 1920 influenzal years, Stokes and Callaway[58] in 1937 pointed out that there were numerous references to the sensitizing effect of the influenza or virus phase to subsequent invasion by pyococci. For example, Chickering and Park[14] called attention to staphylococcic pneumonia as a frequent complication. Small and Stangl[56] isolated streptococci from most of their patients with pneumonia and found staphylococci and pneumococci in some instances. Staphylococcic empyema was a fairly common influenzal sequel in 1919; Ballin[5] and Ransohoff[52] noted it especially at the Cincinnati General Hospital, where pneumococci played little part. Levin[43] found empyema in 5%, otitis media in 12% and sinusitis in 10% of children with influenza. Keeler[36] pointed out that pyogenic otitis media follows mild as frequently as it does severe influenza. Abscess of the lung is rated by Fishberg[20] as especially common and serious as compared with other infections of the respiratory tract following influenza. Burgess and Gormly[10] recognized in a more recent epidemic of mild influenza (1930) that there was a striking rise in the incidence of pneumonia and an increased tendency toward the fulminating type caused by *Staphylococcus aureus*, as in the 1918 epidemic.

The question as to whether the staphylococcal diarrheas which appear in sub-epidemics during periods of influenzal prevalence are to be regarded as associates of the virus infection or merely coincidences is, of course, hardly settled. Attention has been drawn to them in an editorial,[21] and Terrell and Owen[66] subsequently reported a 30-case epidemic. Jankelson and Massell[32] believed the pyogenic lesions of the skin in 5 cases of ulcerative colitis contained the same organism as that obtained from the intestinal lesions. To quote Stokes and Callaway again, "It appears, then, that an induced sensitization to pyococci, whether of virus or of pyococcic systemic (gastro-intestinal) origin, is a fair presumptive sequel of epidemic intercurrent virus infection such as that which occurred during the year 1936 in the eastern part of the United States. During this year 134 instances were observed of an apparently direct relation of pustular flares to intercurrent infections such as the colds, grip, conventional influenza and the gastro-enteritic type of infection. The incidence in female subjects slightly preponderated. One-third of the patients had infections of the upper part of the respiratory tract; one-half had gastro-intestinal infection, and one-fifth had grip. Relapses unexplained by other factors, such as diet, fatigue, negligence, ingestion of alcohol, nervous tension, contacts and climatic conditions, were observed, in order of frequency, in 81 patients with acne vulgaris and acneiform eruptions, in 17 with a mycotic-pyogenic-allergic dermatosis, in 12 with chronic extensive eczema (neurodermatitis), in 6 with pruritus ani et vulvæ, in 6 with dermatophytosis of the feet accompanied with dermaphytids and in a few with seborrheic, rosaceal or furuncular eruptions, an eruption caused by stasis or by a drug, lupus erythematosus or cheilitis.

"It is notable as a first suggestion of the allergic character of this type of relapse that a marked trend toward familial pyogenic susceptibility was observed in the patients, as noted by Stokes and King[60] in their study of acne and seborrheic der-

matoses. This pyogen-predisposed background appeared among patients with allergic eczema in 91%, with dermatophytosis in 84%, with acne in 75% and with pyogenic-mycotic-allergic dermatosis in 70%. A second suggestion of an allergic background for the phenomenon is the latent period, during which sensitization to the pyogenic or pustule-producing agent might take place. In 60% of cases the outbreak began between the 7th and 11th day following the recognized onset of the general infection. Leipner[41] observed a latent period of from 8 to 10 days preceding an epidemic outbreak of erythema multiforme in 30 of 56 boys in a school home, after mild coryza."

In interpreting these observations these authors call attention to the arguments in favor of an allergic background for the phenomenon, including the latent period of 7 to 11 days between the onset of the general infection and the appearance of the pyogenic sequence recognizable in 60% of the cases observed. They further cite the early observations of Stokes and Cathcart[59] on the effect of nasorespiratory infection in causing a swing toward pustulation in previously uncomplicated and relatively mild exfoliative dermatitis, and of Stokes and Kulchar[61] on the infection allergic interplay of both mycotic and pyogenic infection in arsenical exfoliative dermatitis.

On the experimental side of the virus-pyogen sequence, there is a notable paucity of studies. Glover,[28] in his work with the influenza virus in ferrets, called attention to the rôle of streptococci in exploiting, so to speak, a virus infection, implying that the clinical picture was a summation of the effects of both infections. Stuart-Harris[63] comments on the notable lack of attention to the virus pyogen relationship which has marked current thinking, pointing particularly to *Staphlococcus aureus*.

The 3 most recent applications of the virus-pyogen exacerbative sequence have concerned hemolytic-pyogenic and mycotic pyogen infections of the hands; prurigo Besnier (cutaneous phase of the eczema-asthma-hay-fever complex) and the production of photosensitivity. Stokes, Lee and Johnson[62] state that their physician and lay patients recognized the virus pyogen flares of the dermatitis of their hands, as well as did the authors themselves. Provocation of extensive ids was taken as evidence of the allergic basis of the flare. To quote: "Spreading erythema, increased edema, a shower of pustules locally, extension without change in morphology, local lymphangitis and lymphadenitis, sudden involvement of the predisposed flush areas (ears, center face), flexures (intertrigo) or a wholesale outbreak of a follicular papular patchy or diffusely confluent dermatitis, each or severally constitute the flare." Sulfonamides had to be used to control the occasional head to foot outbursts of pustules or a pemphigoid eruption. Norrlind[49] and independently Bøe[9] have apparently applied a concept of induced infection-allergy, to a hypo- or desensitizing treatment with vaccines of the secondary pyogen invader factor in exacerbations produced by nasorespiratory infections, in the eczema phase of the eczema-asthma-hay - fever complex (prurigo Besnier). Stokes and Callaway (1937) described with case illustrations the development of light sensitivity following virus infections, and in a comment on the complexity of the situation involved, noted interrelations between light sensitivity and virus infection, light sensitivity and pyogen flares with or without obvious relation to an outspoken nasorespiratory infection, and virus-pyogen-nickel sensitivity. While they concede the mechanism to be obscure, they venture the suggestion that the light sensitivity in some cases may not be a true allergic affair but be the result of porphyrin absorption from the intestinal tract, where perhaps a perverted (pyogen) flora follows the virus invasion. They invoke this concept also (a hypothetical shift in intestinal bacterial flora following virus infection) to explain in theory the exacerbation of pruritus ani and anal and inguinal intertriginous ecze-

mas following virus respiratory tract infections. It is in fact not inconceivable that catarrhal vulvovaginitis following respiratory virus infections from which micrococcus catarrhalis is recovered is an example of a virus-pyogen sequence.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

NOAH D. FABRICANT, M.D.

ASSISTANT PROFESSOR, DEPARTMENT OF OTOLARYNGOLOGY, UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO, ILLINOIS

THROAT MEDICATION: A SURVEY OF CURRENT TRENDS

By Noah D. Fabricant, M.D.

CHICAGO, ILLINOIS

Although the throat is the site of the most common surgical operation in the world, it has been surprisingly free from that type of intensive physiologic investigation which, with some measure of success, has contributed to the improvement of nasal medication. As in the case of nasal medication, a judicious union between physiology and pharmacology, tempered by comprehensive bacteriologic studies and cemented by sane clinical judgment, can provide a firm foundation for rational throat medication. The more one examines the therapy of the abnormal throat, the more firmly does this thought impress itself.

For purposes of this discussion, the term "throat" is made to apply strictly to the mesopharynx—the region bounded posteriorly by the posterior pharyngeal wall; anteriorly by the base of the tongue and by the open space directed toward the mouth; laterally by the lateral pharyngeal walls; superiorly by the nasopharynx; and inferiorly by the larynx and upper pharyngeal end of the esophagus. Within the mesopharynx lie masses of lymphoid tissue, more or less symmetrically arranged to constitute Waldeyer's ring, which through their tendency to disease produce various acute and chronic inflammations and infections (tonsillitis, pharyngitis, "sore throat," Vincent's angina and lymphoid hyperplasia, to mention an important few). The manner of their treatment is twofold: local and systemic. A survey of current trends in throat medication for non-surgical conditions points to the importance of both approaches.

Rationale of Local Throat Medication. In recent years considerable doubt has been cast on the value of gargles in acute tonsillitis and acute pharyngitis. Although popular with the laity, the use of a gargle has no real therapeutic foundation since, as Richards[23] points out, the very process of gargling necessitates an approximation of the posterior part of the tongue to the soft palate in order to prevent fluids from running into the larynx. Experiments[20] with methylene blue, designed to determine how efficient gargling may be, demonstrate that the dye cannot be seen beyond the third molar tooth and cannot reach the tonsillar areas. Painting the throat in acute infections, on the other hand, is only of psychic value.

According to MacGregor and Long,[17] the efficacy of drugs administered orally as pastilles, lozenges or pills for local treatment of tonsillitis or pharyngitis depends largely on the direction of salivary flow which apparently varies in individuals and with posture. They conducted experiments with pastilles to estimate the amount of penicillin likely to reach affected areas at the back of the mouth. Of 50 subjects studied, some had had their tonsils removed and the rest had tonsils ranging in all degrees of size. The pastilles used were of the same base, shape and size as penicillin pastilles but contained 1% methylene blue instead of 500 units of penicillin. The pastille, for purposes of study, was placed in the mouth in the buccal fold between cheek and teeth and allowed to dissolve without

agitation. The degree of staining of the anterior pillars of the fauces, uvula and tonsils was considerable at the end of 5 minutes and much more at 15 minutes, although the tonsillar area was not as heavily stained as the other 2 sites. The pharynx, when reached, was only slightly stained.

These experiments appear to indicate that, with a gelatin base, dyes reach the tonsillar area to an extent sufficient to suggest that drugs administered in the same type of base should reach the tonsils in most cases. Lack of staining of the pharynx, however, in a large proportion of subjects suggests that any attempt to treat pharyngitis with drugs contained in pastilles or lozenges is often doomed to failure. Flow of saliva at the back of the mouth and the swallowing mechanism appear to be such that saliva does not bathe this region as effectively as the oral cavity.

Arnett[1] believes that drugs incorporated in paraffin are slowly released into the saliva when chewed. During the process of chewing and swallowing they come into intimate contact with the gingiva, the pharynx and the esophagus. In order to determine the extent and degree of mucosal staining produced by the incorporation of methylene blue and gentian violet, observations were made on 13 subjects. While it was found that dyes stained the tongue and gingival margins deeply and the buccal mucosa moderately, the tonsils and the posterior pharyngeal structures were usually unstained when the patient remained in an upright position; however, when the subject chewed and swallowed while in a recumbent position, with head lower than shoulders, the tonsils and posterior pharyngeal tissues usually became stained.

Vollum and Wilson[32] describe an outbreak of scarlet fever due to *Streptococcus pyogenes*, Type II, in a residential preparatory school for boys and an outbreak of sore throat accompanied by cases of scarlet fever due to Type I streptococcus in a residental public school for girls. Treatment of healthy and of convalescent carriers with 6 to 12 lozenges (containing 0.5 gm. sulfapyridine and 0.5 gm. sulfathiazole) a day for 5 to 7 days apparently had no effect in clearing the infecting type of streptococcus from the throat as compared with control carriers receiving either a spray or no treatment. Prophylactic treatment of healthy, non-infected individuals with 6 lozenges daily had no apparent effect in preventing streptococcic infection of the throat. Observations made on persons sucking methylene blue tablets demonstrated that only a fraction of the dye was deposited on the tonsils and none on the posterior pharyngeal wall. The authors, therefore, conclude that neither for prophylaxis nor for cure of streptococcic infection of the throat are lozenges containing sulfonamides likely to be valuable in clinical practice.

A more optimistic note is struck by Rosenthal[25] who finds that penicillin lozenge medication elicits a response superior to that obtainable with a triple dose of penicillin by injection. He finds that a gelatinous throat lozenge gives excellent results in follicular tonsillitis and ulcerous Vincent's angina. The patient is admonished to permit the lozenge to dissolve slowly on the tongue; the medication goes into solution within approximately 15 minutes when the lesions are bathed in a buffered solution of penicillin (2500 units). One lozenge is administered hourly. It is also reported that a chewing wafer of sulfonamide mixture gives excellent results in cases of severe pharyngitis and mild forms of tonsillitis. The patient chews the wafer as he would gum. The inflammatory process usually resolves within 2 or 3 days. In the opinion of Fox and Kesel[7] and their associates, effective topical application of sulfonamide drugs to diseased or injured oropharyngeal tissues has been difficult, mainly because mechanical factors prevent the maintenance of a satisfactory concentration of the drug. The smooth oral mucosa is continually washed by saliva and does not lend itself favorably to treatment by

powders, ointments or solutions. From the standpoint of minimal systemic toxicity and minimal local antibacterial potency, they maintain that sulfathiazole in chewing gum seems to be the preferable local chemotherapy for the infections of pharyngeal and oral mucosa which are susceptible to sulfonamide compounds. Best clinical results are claimed in conditions of the pharynx and mouth in which the beta hemolytic streptococcus is the preponderant etiologic organism. In 52 cases of acute lymphoid pharyngitis and follicular tonsillitis, 72% showed a decided decrease in the total count within 48 hours, along with the complete disappearance of the beta streptococci in the cultures.

It has been asserted by Fantus[6] that a hydrogen ion concentration near that which is normal for the mucous membrane is of even greater importance for applications to the mucous membranes than is isotonicity. So far as concerns the pH values of local medicaments, valid therapeutic conclusions have been drawn in a variety of clinical fields from measurements of the hydrogen ion levels of various secretions found in their original positions on underlying mucous membrane and tissue surfaces. Fabricant[5] finds the normal physiologic range of values for the pH of the mucous membrane of the throat in a large group of men and women with clinically normal throats to be from 4.9 to 8. For 54.8% of the subjects the values were entirely within the acid range; for 7.8%, entirely within the alkaline range, and for 37.4% they fell within a slightly acid, slightly alkaline range of fluctuations. From these observations it is apparent that the normal human throat may be either acid or slightly alkaline. The claims advanced by some pharmaceutic manufacturers that their particular varieties of local throat medicaments "neutralize excess acidity in the mouth and throat" and that therefore they are superior because of this quality can indeed be challenged when it becomes clear that the pH of the mucous membranes of the throat normally is, for the most part, within an acid range.

Results of treatment of 69 patients with acute pharyngeal infections by insufflation of sulfanilamide powder are reported by Goldman and Kiesewetter.[9] The powder was insufflated once a day early in the series and later twice a day. Fifty-four patients with similar conditions were treated by other currently accepted standard methods. The average time required for clinical cure was 1.8 days shorter in patients with acute tonsillitis treated with sulfanilamide powder than in the controls, and 1.7 days shorter in patients with Vincent's ulcerative tonsillitis. The insufflations appeared effective in 9 patients with acute pharyngitis, but this group was deemed too small for comment. About 5 gr. of the sulfanilamide powder was employed at each insufflation. Blood examinations of 16 patients revealed no detectable amount of sulfanilamide. Freeman[8] advocates the local use of sulfathiazole powder for acute pharyngeal infections. Sulfathiazole powder is applied until it thickly cakes the involved areas. It is claimed the method rapidly produces subjective and objective relief and materially shortens the course of the disease. In the experience of Hollender,[10] sulfathiazole powder treatment, as compared with other topical remedies for pharyngitis, gives every indication of being effective in relieving the symptoms more promptly and in shortening the course of the disease. In the chronic cases a number of applications may be necessary and these should be given at intervals of several days.

Struble[31] maintains that in most cases acute pharyngitis responds well to the intelligent use of time-tried methods of treatment, such as rest in bed, irrigations of the throat with hot, isotonic solution of sodium chloride, and carefully controlled treatment with sulfonamide compounds. It has been his custom to continue using these methods and to administer penicillin intramuscularly only when other means of therapy appear to be inadequate.

One method of irrigating the throat

involves supplying irrigating fluid from a container held slightly above the patient's head; the fluid is allowed to run over the tonsils and posterior pharyngeal wall. Syringes and modifications of a douching apparatus can likewise be employed in irrigations of the throat. Marcotte[19] studied 29 patients with symptoms of granular pharyngitis, all of whom presented the typical nodules of hypertrophied lymphoid tissue distributed in varying amounts over the pharyngeal mucosa. Treatment locally consisted of cauterization with a 50% silver nitrate solution or destruction by means of electrocoagulation.

THE USE OF SULFONAMIDES AND PENICILLIN. In upper respiratory tract infections the incidence of hemolytic streptococcus in cultures from the nasopharynx varies from year to year. In army and civilian hospitals in New York City and its environs, the incidence during the winter and spring of 1943–44 was 35.4%, as compared with 5.8% for the previous year. There was also an accompanying increase of acute follicular tonsillitis and pharyngitis, often complicated by peritonsillar abscess, pneumonia and empyema. Owing to the increasing seriousness of these infections, Plummer[22] and his associates made a clinical and bacteriologic study of the effect of penicillin (28 cases), sulfadiazine (11 cases), and no specific therapy (6 cases) on 45 patients acutely ill with tonsillitis or pharyngitis due to Group A (Lancefield) hemolytic streptococcus. Nine patients received intramuscular injections of penicillin for 24 hours. Peritonsillar abscess was a complication in 2 of these patients. After 24 hours of treatment, cultures were negative for hemolytic streptococcus in 8 cases, but after penicillin was discontinued the organisms reappeared in nasopharyngeal cultures. Of 9 patients who received penicillin for 3 to 4 days, there was bacteriologic and clinical relapse in 4 soon after the discontinuance of penicillin. In these 4 individuals large numbers of hemolytic streptococci were found in nasopharyngeal cultures 48 hours after penicillin was stopped and concomitantly a return of pharyngeal swelling, redness and exudate in 2 of the patients as pronounced as at the onset. During the course of sulfadiazine therapy, the hemolytic streptococci in the nasopharynx were reduced in number, but in only 1 of the 8 cases showing many hemolytic streptococci in the initial culture did these organisms disappear, even temporarily; in all 8 patients they were present in the cultures in large numbers soon after the discontinuance of sulfadiazine. Thus, adequate sulfadiazine therapy in acute streptococcus tonsillitis and nasopharyngitis does not always prevent the patient from becoming a carrier. The authors also had several patients with acute tonsillitis who developed peritonsillar abscess or pneumonia and empyema while taking sulfadiazine in adequate and comprehensive amounts.

While evaluating sulfadiazine and penicillin therapy in tonsillitis, nasopharyngitis and scarlet fever on the basis of observations on 210 young men, Spink[29] and his associates studied approximately 2000 cultures from the nose and throat. As a control, neither sulfadiazine nor penicillin was used in the treatment of 102 patients with acute tonsillitis or nasopharyngitis. The utilization of sulfadiazine did not shorten the clinical course of tonsillitis and did not eradicate hemolytic streptococci from the pharynx. However, in very ill patients the severity of the disease appeared to diminish more rapidly than in untreated controls. Total doses of 200,000 units of penicillin administered intramuscularly to patients with severe tonsillitis and nasopharyngitis reduced the severity, and in some instances, apparently shortened the duration of the disease. It was necessary to administer doses of 500,000 to 1,000,000 units of penicillin before eliminating hemolytic streptococci from cultures of throat material for more than a short period. Clinical relapses following the administration of penicillin took place frequently and apparently were related to the reappearance of hemolytic streptococci in the

throat. In the treatment of tonsillitis, penicillin followed by sulfadiazine apparently possessed no advantage over penicillin alone.

In a study of the effect of sulfanilamide in the treatment of sore throat due to hemolytic streptococci, Rhoads and Afremow[24] made observations on 31 patients treated with sulfanilamide and 36 controls treated under similar conditions but without sulfanilamide. They concluded that in the average uncomplicated case of tonsillitis or pharyngitis due to hemolytic streptococci, the advisability of its routine use is questionable. In support of this point of view, Kernan,[14] Richards,[23] and Hughes[12] all question the oral use of sulfonamide compounds in acute uncomplicated diseases of the pharynx. Smith[28] finds penicillin of definite value in the treatment of acute follicular tonsillitis. The clinical response was rapid and it was necessary to administer the drug for from 5 to 7 days. In his series of cases administering the drug by intramuscular injection gave an advantage over medication by mouth. Lierle and Paul[16] gave oral penicillin to 36 cases of acute pharyngitis and acute tonsillitis. All but 6 showed noticeable improvement within 24 to 48 hours. Six who failed to respond after 48 hours were placed on sulfonamide therapy; the entire number improved immediately.

A comparative study of untreated cases and cases treated with sulfathiazole and sulfadiazine is described by Clodfelter[2] who only selected severe cases of acute tonsillitis, the type frequently referred to as "strep throats." The 400 cases selected for study were chosen from over 3000 cases of acute upper respiratory tract infections of such severity as to require hospitalization. Of 175 patients treated with large doses of sulfonamides, 41 ran a course similar to that of untreated patients and were discharged the 5th or 6th day. A secondary rise in temperature occurred in 134 of the treated patients; most of these were discharged the 10th day, the average number of hospital days being 9.7. Clodfelter concludes that use of sulfonamides in severe cases of acute tonsillitis results in a prompt drop in temperature with some relief of symptoms. However, there is usually a secondary rise in temperature at the time untreated patients are being discharged, after an average of 5.3 days of hospitalization. Further, treated patients d'd not feel as well on the 10th day as untreated patients did on the 5th. Other findings strongly suggest that the use of sulfonamides in the treatment of acute "strep" tonsillitis is not only without benefit but is actually detrimental.

In a study to evaluate the rôle of penicillin in the treatment of acute sore throat, Davison[3] observed 28 cases of acute sore throat. The dose of penicillin employed was 20,000 units every 3 hours day and night by intramuscula· injection. No gargles, irrigations, analgesics or antipyretics were utilized. In all but 2 patients the tonsils were present, and in all patients there was tonsillar exudate, edema and diffuse inflammation of the tonsils and pharyngeal wall. In the 2 men who had had previous tonsillectomies, a diffuse follicular pharyngitis was found. The average total dose of penicillin in 27 cases of acute sore throat was 360,000 units over 54 hours. There was 1 re'apse, in which recovery occurred without further penicillin. One case did not respond until sulfadiazine replaced penicillin as the treatment. No complications occurred, either during or after treatment.

Numerous reports appearing in the medical and dental literature indicate that penicillin is an outstanding therapy for the treatment of Vincent's fusospirochetal infection of the throat and mouth. Shallenberger[27] and his associates found that the local application of penicillin solution, 250 to 500 units per cc. of physiologic saline, administered 4 times daily was highly effective in Vincent's angina. Negative smears were obtained in much shorter time than with sulfadiazine lozenges or oxidizing agents such as silver nitrate or oxyphenarsine hydrochloride.

Hopp[11] treated 25 patients for Vincent's angina with sodium penicillin in gelatin capsules, 10,000 units each, 1 being given every 2 hours for 10 doses. Cure was obtained in 24 hours. Similarly, 37 patients were treated for acute follicular tonsillitis and cure was obtained in 3 to 5 days. Schwartz[26] found good response to intramuscular injections of penicillin in Vincent's angina. Joseph[13] also reported excellent results with penicillin therapy in a series of patients with Vincent's ulcers of the tonsils. Eighteen patients received 100,000 units of penicillin parenterally each day in the form of 2 injections. In all 18 patients the lesions cleared completely within 7 days. Manson and Craig[18] advocate the treatment of Vincent's angina with sulfathiazole. The treatment consists of medication with a 0.5 gm. sulfathiazole tablet, dissolved on the tongue, and given every 2 hours during the day and every 4 hours at night.

While bismuth is now seldom employed in the treatment of Vincent's angina, for a number of years various observers have advocated the parenteral use of bismuth preparations in the treatment of acute tonsillitis. Thus, Monteiro[21] advises injection of a bismuth compound for follicular, parenchymatous and catarrhal types of tonsillitis, Lewis[15] administers a bismuth salicylate in oil preparation intramuscularly, and Stovin[30] recommends for acute tonsillitis the administration of the bismuth salt of heptadienecarboxylic acid in suppository form.

That penicillin should be given together with antitoxin in all cases of severe pharyngeal or nasopharyngeal diphtheria is concluded by Dodds[4] from a comparison of results in 2 series of patients treated respectively with antitoxin alone and combined with penicillin. Penicillin dosage was usually 100,000 units in 24 hours, given intramuscularly in divided doses. The author states that although penicillin therapy did not appear to affect the rate of clearance of the membrane, it did apparently reduce the incidence of complications. In the 13 cases treated with the usual doses of antitoxin plus penicillin, 9 cases escaped paralysis, while only 3 developed clinical myocardial involvement. In the 14 cases treated with antitoxin alone, only 4 patients escaped paralysis while 9 developed clinical myocardial involvement. One death from early myocardial failure occurred in each group.

In conclusion, it can be stated unequivocally that the sulfonamides and penicillin enjoy a prominent position in the ranks of throat medication. Their uses, however, are limited by the development of allergic reactions, by the sensitiveness of patients to these drugs, by the acquisition of "sulfonamide-resistance" and "penicillin-resistance" states, and by their ability to mask symptoms. Their abuses, on the other hand, are encouraged by promiscuity and by lack of intelligence in prescribing for patients with throat ailments.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 18, 1947

Factors in the Control of Capillary and Venous Pressure Demonstrated by a Schema. H. C. BAZETT, M.D. (Dept. of Physiol., Univ. of Penna.). A schema is demonstrated which has a circular flow of fluid. By a device originally described by Krogh the stroke volume may be measured. The pump is driven by water derived from a reservoir entering a vessel and compressing a rubber balloon. Control is attained by solenoid valves operated through cams driven by an electric clock motor. The pulse rate remains constant but can be altered by changing the cams. Similarly the ratio of systole to the cycle may be varied as desired. Simulated arteriolar resistances consist of 8 hypodermic needles arranged in parallel so that any number from 1 to 8 may be used. The arteriolar resistance is thus quantitatively known. Venous resistances on the other side of the "capillary" can be regulated and their values may be calculated according to the rate of flow and observed pressure gradients.

The simulated capillaries may be connected at will with fluid reservoirs intended to simulate tissue fluid. When so connected fluid enters the vascular bed from these reservoirs, if the capillary pressure is below that of the reservoir, and leaves the vascular bed for the reservoir, when the reverse relationship holds.

It can be shown that capillary pressure cannot be maintained constant when arteriolar resistance is altered, unless venous resistance is also altered in such a way as to maintain a constant ratio of arteriolar and venous resistances. The actual level of venous pressure attained during flow depends on the basic pressure to which the whole system is filled (direct), the total resistance in the circuit (inverse), and the rate of flow (inverse.) Fluid interchange can modify the basic filling pressure during flow.

Histologic Changes Produced by 2,4-Dimethyl-3-hydroxy-5-hydroxymethylpyridine, an Analogue of Pyridoxine. CHARLES W. MUSHETT, PH.D., ROBERT B. STEBBINS and MARY N. BARTON (Merck Institute for Therapeutic Research, Rahway, N. J.). The administration of 2,4-dimethyl-3-hydroxy-5-hydroxymethylpyridine (desoxypyridoxine) to a variety of laboratory animals, including the chick, has resulted in atrophy and degeneration in the hematopoietic organs, particularly in those of the lymphoid series. These changes, as a rule, were reflected in the peripheral blood picture. Atrophy in the spleen was accompanied by an apparent increase in the reticular and trabecular elements. In the thymus Hassall's corpuscles, as well as the lymphoid tissue, were involved. Further experimentation is indicated before a statement can be made regarding the potential usefulness of this compound in the treatment of tumors of the lymphoid system. Examination of the adrenal glands of treated animals revealed a decrease in Sudanophilic material, even when these glands were larger than normal. Desoxypyridoxine exaggerated certain deficiency symptoms in puppies on a pyridoxine-free diet, but caused a delay in the appearance of other symptoms. Hyperirritability and convulsions, similar to those observed in pyridoxine deficient animals, could be elicited by a single large dose of the vitamin analogue.

Electromyographic Studies of Human Poliomyelitis. ROBERT HODES, PH.D.

(Johnson Foundation and Dept. of Physical Medicine, Univ. of Penna.). Fourteen patients, 7 to 16 years of age, were examined electromyographically. Onset of acute poliomyelitis had occurred 4.5 to 11.5 years previously.

The electromyographic technique consisted of stimulating percutaneously the nerves supplying the muscles of the forearm, hand, leg and foot, and recording the maximal muscle potentials with surface electrodes. The muscle potentials were amplified by a 3-stage, condenser-coupled amplifier and photographed on moving bromide paper from a 5 inch cathode ray tube.

The response of the muscles of poliomyelitis patients to brief repetitive nerve stimulation is abnormal. The potential evoked by the first of a train of stimuli is greater in amplitude and duration than any of the succeeding spikes produced by identical stimuli to the motor nerve. Such an abnormal electromyogram results from failure of some muscle fibers to respond during the course of tetanic excitation. Single motor unit studies show that some of the component muscle fibers of the unit may fail. In addition, entire motor units may drop out of action during repetitive nerve action.

The failure of some muscle fibers to respond is due, at least in part, to an abnormality at the neuromyal junction which results from the disease process. The possibilities of impaired nerve and muscle function are not excluded.

Prostigmine (1 to 1.5 mg. intramuscularly) restores the electromyogram towards normal (6 patients). The effects of this drug should be studied in a larger series of patients for its possible therapeutic use as a partial restorative of muscle power and as a deterrent to fatigue.

Our experiments demonstrate the existence of peripheral defects in poliomyelitis and require that current concepts of its pathology be broadened to include not only the central nervous system but also those peripheral structures whose activity bring about muscular contraction.

A Study of the Factors Controlling the Differentiation of Mauthner's Cell in Amblystoma. JEAN PIATT, PH.D. (Dept. of Anatomy, Univ. of Penna.). Mauthner's cell in amblystoma occurs at the level of the eighth nerve roots and is in close anatomic and functional relationship with these roots, also the seventh and tenth lateral-line roots. The consistent association between this giant neuron and the vestibular and lateral-line roots suggests the possibility that this relationship may be one of cause and effect, *i. e.*, Mauthner's cell may differentiate under the influence of the eighth or lateral-line nerve roots. A greatly varied series of experiments was carried out on amblystoma punctatum embryos to test this thesis.

Mauthner's cell failed to differentiate in about one-third of those cases in which the eighth roots were prevented from developing. A supernumerary Mauthner's cell developed in a few cases in which experimentally induced ectopic seventh, tenth lateral-line and eighth roots entered the brain at heterotopic levels, more frequently in association with the eighth. Neither consistent nor positive results accrued in many cases but the data, on the whole, indicate that the differentiation of Mauthner's cell is influenced to some extent by the presence of eighth, chiefly, and perhaps also seventh and tenth lateral-line nerve roots. A total of 212 experimental animals was individually studied and form the basis for these tentative conclusions.

BOOK REVIEWS AND NOTICES

ELECTROCARDIOGRAPHY IN PRACTICE. By ASHTON GRAYBIEL, M.D., CAPT., MC, USNR, Co-ordinator of Research, U. S. Naval School of Aviation Medicine, Pensacola, Fla.; and PAUL D. WHITE, M.D., Lecturer in Medicine, Harvard Medical School, Physician, Massachusetts General Hospital. 2nd ed. Pp. 458; 323 ills. Philadelphia and London: W. B. Saunders, 1946. Price, $7.00.

THE authors state that this edition was made necessary primarily because of recent advances in the science of clinical electrocardiography. Much material on precordial leads has been added. The general format and style have not been altered. The method of presentation used throughout the book is to introduce each subject with a brief discussion of pertinent electrocardiographic characteristics and then demonstrate them by means of case reports. In these the interpretation of the electrocardiogram is discussed prior to the presentation of clinical data. The last step is correlation of the 2. The book offers an excellent introduction to electrocardiography because the authors know their subject, the discussion is simple, points of controversy are clearly stated, and the field of clinical electrocardiography is well covered. C. W.

RENAL HYPERTENSION. By EDUARDO BRAUN-MENENDEZ, JUAN CARLOS FASCIOLO, LUIS F. LELOIR, JUAN M. MUNOZ and ALBERTO C. TAQUINI, Institute of Physiology, Faculty of Medical Sciences and Institute of Cardiology, V. F. Grego Foundation, Buenos Aires, Argentina. Translated by Lewis Dexter. Pp. 441; 93 ills. Springfield, Ill.: C. C Thomas, 1946. Price, $6.75.

THE authors' intention is to present a complete and balanced review of the renal aspects of hypertension, experimental and clinical. Their own contributions to knowledge of experimental hypertension more than justify the inclusion of a preponderance of their own data. However, nothing can justify evident emotional bias in their discussions of other investigations and investigators.

The short section on clinical hypertension is obviously second-hand and carries none of the conviction of the experimental. It is therefore not recommended to clinicians. On the other hand, the book will be useful to investigators, even though it is a disappointment to those who had hoped for a balanced treatment of this important subject. The Reviewer still thinks that this excellent group of investigators is capable of giving one. The Bibliography is thorough. The publisher has shown his usual attention to the niceties of bookmaking. I. P.

RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.D., M.A. Pp. 415; 76 ills. Philadelphia: Blakiston, 1946. Price, $5.00.

THE various endocrine glands of the body are considered in the light of chemistry, physiology, pathology and clinical manifestations and treatment of endocrine disturbances. Much emphasis is placed on therapy. Pathologic aspects are short and sometimes incomplete. Clinical manifestations of alterations in the pituitary, thyroid, parathyroid, adrenals, islets of Langerhans, and reproductive glands are given thorough consideration. There is a separate short discussion of gastro-intestinal hormones, pineal gland, rennin and antihormones. The book is especially valuable to the clinician because of its lengthy diagnostic and therapeutic aspects. I. Z.

GENERAL BIOLOGY. By WILLIAM C. BEAVER, Professor of Biology, Wittenberg College, Springfield, Ohio. 3rd ed. Pp. 820; 325 ills. St. Louis: C. V. Mosby, 1946. Price, $4.75.

THE text material is presented in 4 parts. Part I deals with protoplasm and the general morphology and physiology of plant and animal cells. Part II includes a survey of the animal kingdom and the physiology of the organ systems of man from a phylogenetic approach. A similar procedure is followed for the plant kingdom in Part III. Part IV discusses the interdependence of living organisms, ecology, paleontology, heredity, evolution and biochemical and biophysical phenomena, with discussions of biology in relation to medicine, economics

and so on, and a very brief review of the history of biology. A 5th section includes a list of combining forms and a glossary. The book is well indexed.

The phylogenetic arrangement of the physiology of the organ systems leads to repetition and the details of the text tend to conceal the general ideas and concepts of biology which the non-specializing student should carry away from a general course.

After reading this text through, one gets the impression of having gleaned a smattering of facts about all fields of biology but no real understanding of any. M. McC.

MEDICAL EDUCATION AND THE CHANGING ORDER. By RAYMOND B. ALLEN, Executive Dean, Colleges of Dentistry, Medicine and Pharmacy, University of Illinois. Pp. 142. New York: Commonwealth Fund, 1946. Price, $1.50.

PREPARATION of this monograph was assigned to the author by the Committee on Medicine and the Changing Order of the New York Academy of Medicine. It is a discussion of medical education in America, and especially of the changes to be desired in the light of contemporary social progress. The author advocates a pre-medical education which offers opportunities for adequate preparation in the biologic and physical sciences, but avoids the dangers of too great concentration in pure science in order to allow sufficient time for studies in social science and the humanities. In the Medical School, he advocates lifting medical education above the level of mere training in the technology of medical practice. He desires more and better training in logical thinking, and in deductive and inductive reasoning. He would increase the emphasis given to the relation between the practice of medicine and community needs. He seeks to make the internship an experience in the practice of preventive as well as of curative medicine, and to include in it family medicine as well as hospital and out-patient department medicine. He would organize residency and fellowship programs to place the responsibility for the student's progress and achievement squarely on the student himself. He is an advocate of increasing the programs of postgraduate teaching in the light of experience with the courses for returning veterans.

The program envisioned is an attractive one. It is not, of course, original with the author, but seems an able statement of the present trends in American medical education. Let us hope his wishes can be realized.

I. S.

ENVIRONMENTAL WARMTH AND ITS MEASUREMENT. A Book of Reference Prepared for the Royal Naval Personnel Research Committee of the Medical Research Council. By T. BEDFORD, D.Sc., PH.D., M.I.MIN.E., Habitability Sub-Committee, the Royal Naval Personnel Research Committee. With a Preface by SURGEON VICE-ADMIRAL SIR SHELDON DUDLEY, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S., K.H.P. Pp. 40; 10 ills. London: His Majesty's Stationery Office, 1946. Price, 70 cents.

THIS war manual was prepared for the information of Ships' Surgeons of the Royal Navy, but should be of interest to the specialist in the field. Citation of chapter headings suffices to indicate the ground covered: body-heat production and heat-loss; instrumental measurements; effective temperature and corrected effective temperature; procedure in making tests; ventilation reports; work at extreme temperatures. W. S.

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